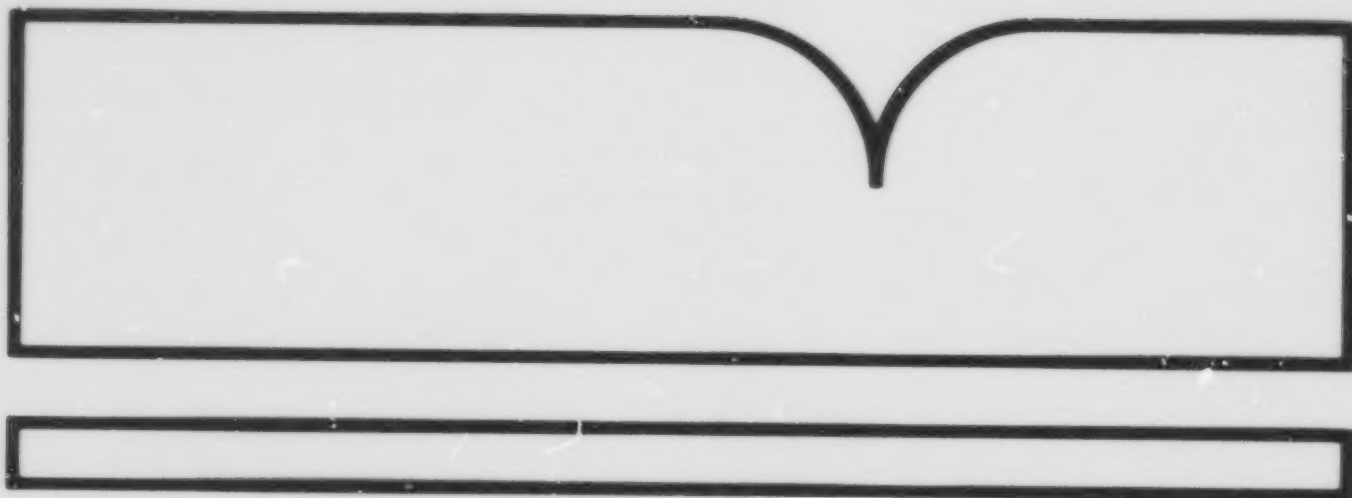


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Health and Environmental Effects
Profile for Methyl Bromide

(U.S.) Environmental Protection Agency
Cincinnati, OH

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16. ABSTRACT The Health and Environmental Effects Profile for <u>Methyl Bromide</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Methyl bromide</u> has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for <u>methyl bromide</u> is <u>0.0014 mg/kg/day</u> for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for <u>methyl bromide</u> is <u>100</u>.		
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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR METHYL BROMIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3112. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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EXECUTIVE SUMMARY

Methyl bromide is a colorless gas at ordinary room temperatures and conditions; it is also a colorless, volatile liquid that boils at 3.56°C under atmospheric pressure (Stenger, 1978). In 1977, production of methyl bromide in the United States was 34.68 million pounds (USITC, 1978); demand for methyl bromide in the United States was estimated to be 45 million pounds in 1984 (CMR, 1985). Currently, only two companies in the United States (Ethyl Corp. and Great Lakes Chem.) manufacture methyl bromide. Methyl bromide is predominantly used as a soil and space fumigant to control fungi, nematodes, weeds, insects and rodents; it is also used by the chemical industry as a methylating agent (CMR, 1985; Stenger, 1978).

Volatilization and hydrolysis are the two important fate mechanisms for methyl bromide in water. Using an experimentally determined mass transfer coefficient for the transport of methyl bromide to air (Neely, 1976), the volatilization half-life in a pool of water 1 m deep can be calculated to be 3.1 hours (Lyman et al., 1982). Volatilization half-lives of 1-5 days can be calculated for average ponds, rivers and lakes using a reaeration rate ratio determined by Mabey et al. (1981), although the half-life may be significantly longer in deep bodies of water. Based on experimental data, the hydrolytic half-life of methyl bromide in water at 20-25°C can be calculated to be on the order of 20-38 days (Mabey and Mill, 1978; Castro and Belser, 1981; Ehrenberg et al., 1974). Aquatic photolysis, oxidation, biodegradation, adsorption and bioaccumulation are not expected to be significant.

In the troposphere, the main route of methyl bromide degradation is reaction with hydroxyl radicals (Robbins, 1976); calculated half-lives are

on the order of 0.5-1.0 year for typical atmospheres (see Table 2-2). At this decomposition rate, ~3% of the tropospheric methyl bromide is expected to diffuse eventually into the stratosphere (Callahan et al., 1979). Upon reaching the stratosphere, the methyl bromide is expected to undergo direct photolysis (Robbins, 1976); direct photolysis does not occur in the troposphere because methyl bromide does not absorb light >290 nm (Robbins, 1976).

Volatilization is the dominant fate mechanism for methyl bromide in soil (Sanborn et al., 1977; Jury et al., 1984; Brown and Rolston, 1980). Small amounts of methyl bromide are chemically transformed in soil with the amount of transformation to bromine ions increasing with an increase in soil organic content (Brown and Rolston, 1980). Significant leaching of methyl bromide has been demonstrated in greenhouse soils (Wegman et al., 1981; Vanachter et al., 1981) and in adsorption studies with various soil types (Daelemans and Siebering, 1977). Methyl bromide is considered a nonpersistent pesticide in soil (Sanborn et al., 1977).

Methyl bromide has been detected in drinking water (Kool et al., 1982; U.S. EPA, 1975; Shackelford and Keith, 1976), groundwater (Greenberg et al., 1982), and seawater (Singh et al., 1977a, 1983; Lovelock, 1975). The presence of methyl bromide in seawater appears to be from natural formation (Singh et al., 1977a, 1983), and the release of methyl bromide from seawater to the atmosphere may be the dominant route of its atmospheric exposure (Singh et al., 1983). Water chlorination treatment is capable of forming bromo-organic compounds such as methyl bromide (Gould et al., 1983) and may contribute to the presence of methyl bromide in finished drinking waters. Although used as a fumigant for food products, methyl bromide disappears from fumigated foods within a few days, leaving only inorganic bromide residues (Stenger, 1978). Extensive monitoring of foods by Federal programs

has resulted in infrequent detection of methyl bromide (Duggan et al., 1983). Atmospheric monitoring studies have detected methyl bromide in urban air, rural air, oceanic air, Arctic air, the stratosphere and near manufacturing plants (see Table 3-1). In addition to the atmospheric exposure resulting from seawater, methyl bromide is also emitted to the air as a result of fumigant uses (U.S. EPA, 1985) and automobile exhaust (Harsch and Rasmussen, 1977).

Methyl bromide was absorbed following oral (Medinsky et al., 1984) and inhalation (Medinsky et al., 1985; Gargas and Andersen, 1982; Bond et al., 1985) exposure of rats. Of an orally administered dose, at least 93% was absorbed (Medinsky et al., 1984). At low inhalation exposure levels (<540 mg/m^3) for 6 hours, ~50% of the inhaled methyl bromide was absorbed, and absorption followed first-order kinetics (Medinsky et al., 1985). At a higher exposure level (987 mg/m^3), methyl bromide absorption followed second-order kinetics. Noting that glutathione conjugation may be a major metabolic pathway for methyl halides (Kornbrust and Bus, 1983), Medinsky et al. (1985) suggested that absorption may depend upon duration of exposure and that the rate-limiting factor may be the availability of glutathione. Especially, since according to Gargas and Andersen (1982), transpulmonary absorption followed first-order kinetics at high exposure levels (765 - 3588 mg/m^3 for 2 hours). The highest relative concentrations of methyl bromide occurred in the lungs, kidneys, liver and stomach after either oral or inhalation exposure (Medinsky et al., 1984; Bond et al., 1985). The liver contained the highest concentration of methyl bromide after oral exposure (Medinsky et al., 1984), whereas the lungs contained the highest concentration of methyl bromide after inhalation exposure (Bond et al., 1985). The longest half-life of methyl bromide occurred in the liver, followed by the

blood and the testes after inhalation exposure (Bond et al., 1985). Methyl bromide may react with sulfhydryl groups and therefore with glutathione (Medinsky et al., 1984). Biliary excretion of S-methylglutathione is followed by reabsorption of S-methylglutathione and metabolizes further to substances eliminated by the lungs or kidneys. Collection of bile during the 24 hours following oral dosing of rats resulted in the recovery of 46% of the administered radioactivity (Medinsky et al., 1984). Urinary excretion was the main route of elimination after oral administration, whereas pulmonary excretion was the main route of elimination after inhalation exposure (Medinsky et al., 1984; Bond et al., 1985). Following oral dosing, excretion in the urine and expired air was biphasic. Following inhalation exposure, urinary excretion followed first order kinetics, but pulmonary excretion followed second-order kinetics (Medinsky et al., 1985; Bond et al., 1985).

The preliminary study of a chronic inhalation study in rats and mice is in progress (NTP, 1985). Although Danse et al. (1984) reported that 50 mg/kg/day of methyl bromide caused carcinoma of the forestomach in rats treated by gavage 5 days/week for 13 weeks, the NTP scientists that reviewed the data concluded that the rats treated with 50 mg/kg/day of methyl bromide had epithelial hyperplasia and inflammation in the forestomach but no neoplastic lesions (U.S. EPA, 1984a, 1985). Tumors did not occur at any other dose level tested. An epidemiological study (Wong et al., 1984) suggests that occupational exposure to methyl bromide may be associated with a significantly higher incidence of testicular cancer than expected, but exposure levels were not quantified.

Methyl bromide was mutagenic to *S. typhimurium* strain 100, but not to strain 98, regardless of metabolic activation (Voogd et al., 1982; Moriya et

al., 1983; Kramers et al., 1985; Simmon, 1978, 1981; Simmon and Tardiff, 1978; Simmon et al., 1977), and to E. coli (Moriya et al., 1983; Djalali-Behzad et al., 1981). Thus, the mutagenicity of methyl bromide in bacteria is consistent with its alkylating properties (Djalali-Behzad et al., 1981) in that it is a direct-acting mutagen that produces primarily base-pair mutations. It also produces sex-linked recessive lethals in D. melanogaster (Voogd et al., 1982; Kramers et al., 1985; McGregor, 1981; Katz, 1985; Kramers and Bissumbhar, 1983). The only mutagenicity assay performed with mammalian cells was the mouse lymphoma cell assay in which methyl bromide was mutagenic at two different loci (Voogd et al., 1982; Kramers et al., 1985). Methyl bromide did not increase unscheduled DNA synthesis in cultured mammalian cells (Voogd et al., 1982; Kramers et al., 1985), sperm abnormalities in mice (McGregor, 1981) or chromosomal abnormalities in bone marrow cells in rats (McGregor, 1981).

Methyl bromide was not teratogenic, fetotoxic or maternotoxic in rats exposed by inhalation to ≤ 70 ppm (272 mg/m³), 7 hours/day during gestation (Hardin et al., 1981; Sikov et al., 1980). In rabbits, however, methyl bromide was maternotoxic, causing a high mortality rate at an inhalation exposure concentration of 70 ppm (272 mg/m³), 7 hours/day, 5 days/week during gestation, but did not appear to be fetotoxic (Hardin et al., 1981; Sikov et al., 1980). No evidence of teratogenic effects were observed in rabbits. Pertinent data regarding other reproductive effects of methyl bromide could not be located in the available literature as cited in the Appendix.

Subchronic inhalation of methyl bromide 7.5-8 hours/day, 5 days/week resulted in convulsions, weight loss and pathological changes in the lungs of rats at 0.42 mg/l, paralysis and pulmonary disease in rabbits at ≥ 0.13

mg/l, paralysis and convulsions in monkeys at ≥ 0.25 mg/l and pulmonary lesions and death in guinea pigs at ≥ 0.42 mg/l (Irish et al., 1940). Subchronic treatment of rats by gavage 5 days/week with methyl bromide resulted in severe epithelial hyperplasia in the forestomach at a dose of 50 mg/kg/day and slight epithelial hyperplasia in the forestomach at a dose of 10 mg/kg/day (Danse et al., 1984). At 50 mg/kg/day, decreased food consumption and body weight gain, and anemia were observed in the male rats and slight pulmonary atelectasis was observed in both male and female rats (Danse et al., 1984).

Little information is available concerning the effects of methyl bromide on aquatic organisms. LC_{50} values of 11, 12 and 17 mg/l have been reported for bluegills, tidewater silversides (Dawson et al., 1977) and carp, respectively (Segers et al., 1984).

The application of an uncertainty factor of 1000 resulted in the derivation of a provisional ADI of 0.0014 mg/kg/day or 0.098 mg/kg for a 70 kg man. This ADI was derived from a subchronic oral NOEL of 2 mg/kg/day, 5 days/week in rats in the study by Danse et al. (1984). Higher doses (≥ 10 mg/kg/day) apparently resulted in only hyperplasia of the forestomach (U.S. EPA, 1984a). The ADI is provisional pending the results of the inhalation carcinogenicity study in rats and mice, which is currently in progress (NTP, 1985). Some very limited evidence exists that occupational exposure to methyl bromide may increase the risk of testicular cancer (Wong et al., 1984). However, this study is inadequate for carcinogenic risk assessment of methyl bromide since exposure to workers was confounded by other organic bromides, some of which are suspected carcinogens, and since no exposure levels were quantitated. Therefore, methyl bromide is classified as a CAG Group D chemical because of a lack of adequate evidence of carcinogenicity.

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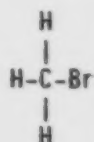
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BUN	Blood urea nitrogen
CAS	Chemical Abstract Service
CS	Composite score
EEG	Electroencephalogram
K _{oc}	Soil sorption coefficient standardized with respect to organic carbon
K _{ow}	Octanol/water partition coefficient
LC ₅₀	Concentration lethal to 50% of recipients
LD ₅₀	Dose lethal to 50% of recipients
MED	Minimum effective dose
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RQ	Reportable quantity
RV _d	Dose-rating value
RV _e	Effect-rating value
TLV	Threshold limit value
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Methyl bromide is known also by the synonyms bromomethane and monobromomethane and by the tradenames, Terabol® and Embafume®. The structure, molecular weight, empirical formula and CAS Registry number for methyl bromide are as follows:



Molecular weight: 94.95

Empirical formula: CH_3Br

CAS Registry number: 74-83-9

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methyl bromide is a colorless liquid or gas with practically no odor (Slenger, 1978), although at high concentrations the odor of the gas has been described as chloroform-like (Worthing and Walker, 1983). Liquid methyl bromide is miscible with most organic solvents (Slenger, 1978). Water solubility varies with pressure; at normal atmospheric pressure (methyl bromide plus water vapor), the solubility at 20°C is 1.75 g/100 g solution. Selected physical properties of methyl bromide are listed below:

Melting point:	-93.7°C	Slenger, 1978
Boiling point:	3.56°C	Slenger, 1978
Specific gravity (0°C):	1.73	Verschueren, 1983
Vapor density:	3.27	Verschueren, 1983
Water solubility:		
at 20°C	17,500 ppm	Slenger, 1978
at 20°C	18,040 ppm	Mackay and Shui, 1981
at 25°C	13,400 ppm	Worthing and Walker, 1983

Vapor pressure (mm Hg):		
at 20°C	1420	Stenger, 1978
at 23.3°C	1520	Perry and Green, 1984
Log K _{ow} :	1.19	Hansch and Leo, 1985
Ionization constants (20°C):	pK not environ- mentally relevant	Mabey et al., 1981
Air conversion factors:	1 mg/m ³ = 0.26 ppm	

Methyl bromide hydrolyzes in water to yield methanol and hydrobromic acid; hydrolysis proceeds more rapidly in alkalies (Stenger, 1978). Methyl bromide can be used effectively to methylate amines and sulfur compounds (Stenger, 1978). In ice water, methyl bromide forms a crystalline hydrate (Worthing and Walker, 1983).

1.3. PRODUCTION DATA

The most recent U.S. production volume reported for methyl bromide is 34.68 million pounds in 1977 (USITC, 1978). American demand in 1984 and 1985 was estimated as 45 and 42.5 million pounds, respectively (CMR, 1985).

The current United States manufacturers of methyl bromide are:

<u>Manufacturers</u>	<u>Annual Capacity (millions of pounds)</u>
Ethyl Corp. (Magnolia, AR)	7
Great Lakes Chem. (El Dorado, AR)	36

Dow Chemical closed its 21 million pound/year plant at Midland, MI, in August 1983 (CMR, 1985). Commercial production methods are based primarily upon the reaction of methanol with hydrobromic acid (Stenger, 1978).

1.4. USE DATA

The use-pattern for methyl bromide has been reported as follows (CMR, 1985):

Soil fumigant	65%
Space fumigant	15%
Chemical processes	10%
Exports	10%

As a soil fumigant, methyl bromide is used to control fungi, nematodes and weeds (Worthing and Walker, 1983). It is used in the space fumigation of food commodities and storage facilities and in insect and rodent extermination (Stenger, 1978). In the chemical industry, methyl bromide is used as a methylating agent in the preparation of aniline dyes and other compounds (U.S. EPA, 1985). It can also be used as a solvent for the extraction of oils from nuts, seeds and flowers, and for degreasing wool.

1.5. SUMMARY

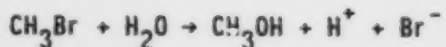
Methyl bromide is a colorless gas at ordinary room temperatures and conditions; it is also a colorless, volatile liquid that boils at 3.56°C under atmospheric pressure (Stenger, 1978). In 1977, production of methyl bromide in the United States was 34.68 million pounds (USITC, 1978); the demand for methyl bromide in 1984 was estimated to be 45 million pounds in the United States (CMR, 1985). Currently, only two companies in the United States (Ethyl Corp. and Great Lakes Chem.) manufacture methyl bromide. Methyl bromide is predominantly used as a soil and space fumigant to control fungi, nematodes, weeds, insects and rodents; it is also used by the chemical industry as a methylating agent (CMR, 1985; Stenger, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Hydrolysis rates for methyl bromide under neutral pH conditions are listed in Table 2-1; the hydrolytic half-life at 20-25°C is on the order of 20-38 days. Thus, at these temperatures hydrolysis is likely to be a significant removal process. In very cold waters, however, the hydrolysis rate will be significantly slower, perhaps by an order of magnitude or more.

At neutral pH, hydrolysis of methyl bromide proceeds as shown below (Castro and Belser, 1981):



Hydrolysis in basic solution is not significantly faster below a pH of 10 (Mabey and Mill, 1978).

2.1.2. Oxidation. The oxidation of methyl bromide in water is not expected to be significant, based on reaction rates with peroxy radicals and singlet oxygen (Mabey et al., 1981; Callahan et al., 1979).

2.1.3. Photolysis. Pertinent data regarding the photolysis of methyl bromide in water could not be located in the available literature as cited in the Appendix. Methyl bromide does not significantly absorb light >290 nm (Robbins, 1976; Mabey et al., 1981); therefore, direct photolysis in the environment is not an important fate process.

When Castro and Belser (1981) irradiated an aqueous solution of methyl bromide with a 254 nm light, the hydrolysis rate increased nearly 7-fold. The irradiation spectrum of the light, however, is not relevant to surface waters.

TABLE 2-1
Hydrolysis Rates for Methyl Bromide in Neutral pH Conditions

Temperature (°C)	Rate Constant (sec ⁻¹)	Calculated Half-life (days)	Remarks	Reference
25	4.09x10 ⁻⁷	19.6	rate constant calculated from experimental data generated at higher tem- peratures	Mabey and Mill, 1978
20 37	2.11x10 ⁻⁷ 2.19x10 ⁻⁶	38.0 3.7	rate constants calculated from experimental data generated at higher tem- peratures	Ehrenberg et al., 1974
25	3.0x10 ⁻⁷	26.7	experimental data	Castro and Belser, 1981
50	1.1x10 ⁻⁵	0.7	experimental data	Heppolette and Robertson, 1966

2.1.4. Microbial Degradation. Pertinent data regarding the biodegradation of methyl bromide were limited. Methylotrophic bacteria have demonstrated an ability to oxidize methyl bromide (Haber et al., 1983; Patel et al., 1982; Stirling and Dalton, 1979, 1980). Patel et al. (1982) demonstrated that soluble methane monooxygenase, isolated from the facultative methane utilizing organism Methylobacterium sp. CRL-26, oxidized methyl bromide to yield formaldehyde. Similarly, Stirling and Dalton (1979, 1980) found that both cell-free extracts and whole-cell suspensions of Methylococcus capsulatus (bath) were capable of oxidizing methyl bromide to yield formaldehyde. M. capsulatus was not able to grow on methyl bromide, however; this is probably due to the toxicity of bromide ions produced from the dismutation of bromoethanol to formaldehyde (Stirling and Dalton, 1980).

Although substantive data could not be located in the available literature, biodegradation is probably not a significant fate mechanism (Callahan et al., 1979).

2.1.5. Volatilization. The mass transfer coefficient for the transport of methyl bromide from water to air has been experimentally measured to be 22.56 cm/hour at 25°C (Neely, 1976). The volatilization half-life for methyl bromide has been calculated to be 3.1 hours from a water body 1 m deep, using this 22.56 cm/hour value (Lyman et al., 1982).

Mabey et al. (1981) have calculated the reaeration rate ratio for methyl bromide to be 0.737. Using representative oxygen reaeration rates from typical water bodies, the following half-lives are calculated for various aquatic environments at 25°C:

pond	5 days
river	1 day
lake	3.9 days

The calculated Henry's Law constant at 20°C (1.3×10^{-2} atm·m³/mole, Lyman et al., 1982) indicates that volatilization of methyl bromide from water to the atmosphere will be rapid.

2.1.6. Adsorption. Pertinent data regarding the sorption of methyl bromide to particulate organic matter or sediment in water could not be located in the available literature as cited in the Appendix. The relatively high water solubility (17,500 ppm at 20°C) and the tendency of methyl bromide to volatilize from water suggest that sorption in the aquatic environment is not important.

2.1.7. Bioaccumulation. Estimation of the BCF of an organic chemical can be made from the following recommended regression equations (Lyman et al., 1982):

$$\text{Log BCF} = 0.76 \log K_{ow} - 0.23 \quad (2-1)$$

$$\text{Log BCF} = 2.791 - 0.564 \log \text{WS (in ppm)} \quad (2-2)$$

For methyl bromide, the BCF values calculated from Equations 2-1 and 2-2 are 4.7 and 2.5, respectively, based on a $\log K_{ow}$ of 1.19 and a water solubility of 17500 ppm. These BCF values indicate that methyl bromide is not expected to bioaccumulate significantly in aquatic organisms.

2.1.8. Persistence. Wagman et al. (1981) measured the decline of methyl bromide from the water of a surface drainage ditch (0.8 m deep) under environmental conditions. The average half-life for the decline was calculated to be 6.6 hours at a water temperature of -11°C.

2.2. AIR

2.2.1. Reaction with Hydroxyl Radical. In the troposphere, the main route of methyl bromide degradation is reaction with hydroxyl radicals (Robbins, 1976). Table 2-2 lists various values for the rate constant of this reaction and predicted tropospheric residence times and half-lives.

TABLE 2-2

Atmospheric Reaction Rates of Methyl Bromide with Hydroxyl Radical

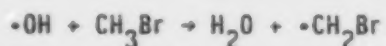
Temperature (°C)	Rate Constant $\times 10^{14}$ (cm ³ /molecule-sec)	Calculated Tropospheric Residence Time* (years)	Calculated Half-life* (days)	Remarks	Reference
23	3.5	0.9	0.63	none	Howard and Evenson, 1976
52	6.08	NA	NA	none	Davis et al., 1976
25	4.14	0.77	0.53		
0	3.16	NA	NA		
-29	2.01	NA	NA		
7	3.2	1.7	NA	residence time calculated by analogy to CH ₃ CCl ₃ residence time prediction	Makide and Rowland, 1981
27	4.0	0.79	0.55	none	Singh et al., 1981
-8	2.74	2.9	NA	residence time calculated on basis of 4×10^{15} OH molecules/cm ³	Singh et al., 1979

*Residence time = $1/\text{rate constant}$; half-life = $0.6931/\text{rate constant}$. Calculations based on a 24-hour average OH concentration of 1×10^5 molecules/cm³.

NA = Not available

The calculated half-lives, which fall between 0.5 and 1.0 year, are an average value only for a typical atmosphere. The rate of reaction can vary by one order of magnitude between winter and summer conditions (Allshuller, 1980).

The reaction between methyl bromide and the OH radical may proceed as follows (Callahan et al., 1979):



It is presumed that the $\cdot\text{CH}_2\text{Br}$ radical will react initially with O_2 and ultimately produce bromine atoms or BrO radicals (Alkinson et al., 1979).

2.2.2. Reaction with $\text{O}(^3\text{P})$ Atoms. The reported rate of reaction between methyl bromide and $\text{O}(^3\text{P})$ atoms at 25°C is 1.4×10^{-16} $\text{cm}^3/\text{molecule-sec}$ (Herron and Hule, 1973). Assuming an average atmospheric $\text{O}(^3\text{P})$ concentration of 5×10^4 molecules/ cm^3 , a half-life of ~3000 years is calculated, and this value does not seem to be environmentally significant.

2.2.3. Photolysis. Methyl bromide does not absorb light >290 nm, therefore, direct photolysis in the troposphere does not occur (Robbins, 1976); however, molecules having tropospheric lifetimes similar to that of methyl bromide diffuse well into the stratosphere (Allshuller, 1980). Given a troposphere-to-stratosphere turnover lifetime of 30 years, based on a tropospheric lifetime of 1 year (Callahan et al., 1979), ~3% of the tropospheric methyl bromide can be expected to reach the stratosphere eventually. Upon reaching the stratosphere, the methyl bromide is expected to undergo direct photolysis because the ozone layer is not present to remove light <290 nm (Robbins, 1976). Thus, photolysis will be the dominant loss mechanism for ≥ 25 km methyl bromide into the atmosphere.

2.2.4. Physical Removal Processes. Physical removal of methyl bromide from the atmosphere is not expected to be significant because methyl bromide, which undergoes dissolution into clouds or experiences wash-out, is likely to re-volatilize into the air.

2.3. SOIL

2.3.1. Volatilization. Methyl bromide is lost primarily into the air after soil fumigation (Sanborn et al., 1977). Jury et al. (1984) used a soil chemical screening model to predict that methyl bromide is a very short-lived compound in soil, with a volatilization half-life of 0.2 days when applied 1 cm deep and a volatilization half-life of 0.5 days when applied 10 cm deep. Brown and Rolston (1980) used soil column tests with a variety of soils to conclude that most methyl bromide used in soil fumigation enters the atmosphere, although some methyl bromide is chemically transformed.

2.3.2. Chemical Transformation. In their soil column tests, Brown and Rolston (1980) found that a small amount of methyl bromide gas is transformed into bromine ions. Clay particles and soil organic matter are reported to be important in the degradation of the compound; as the organic content of soil increases, the amount of methyl bromide transformed into bromine ions also increases. The proposed mechanism of the degradation is the transference of the methyl group of the methyl bromide to the carboxyl groups and N- and S-containing groups of the amino acids and proteins of soil organic matter (U.S. EPA, 1985; Brown and Rolston, 1980; Sanborn et al., 1977).

2.3.3. Adsorption, Leaching and Diffusion. Significant leaching of methyl bromide has been demonstrated in fumigated greenhouse soils (Wegman et al., 1981; Vanachler et al., 1981). Daelemans and Stebering (1977)

tested the adsorption of methyl bromide in loamy sand, loam, and peaty clay soil with calculated K_{oc} values of 1.0, 10.0 and 9.5, respectively, indicating very high soil mobility of methyl bromide. Fuhr et al. (1948) found no adsorption of methyl bromide to a sandy clay soil (11% moisture) after 1 hour of exposure in a chamber.

Abdalla (1973) found soil type to be an important factor affecting diffusion of methyl bromide vapor in soil. Diffusion was more rapid in loamy sand than in a sandy clay or silty loam. Diffusion through the three soil types decreased when soil moisture content was near saturation. Sanborn et al. (1977) reported that methyl bromide sorption is greatest in peat and least in sand.

2.3.4. Persistence. Methyl bromide is considered a nonpersistent pesticide in soil because its disappearance rate is sufficiently rapid (Sanborn et al., 1977). Suess and Lepschy (1979) fumigated both high-humus and low-humus soils with methyl bromide; 12-20 days after fumigation, less than 1 ppm methyl bromide was detectable in dry soil samples.

2.4. SUMMARY

Volatilization and hydrolysis are the two important fate mechanisms for methyl bromide in water. Using an experimentally determined mass transfer coefficient for the transport of methyl bromide to air (Neely, 1976), the volatilization half-life in a pool of water 1 m deep can be calculated to be 3.1 hours (Lyman et al., 1982). Volatilization half-lives of 1-5 days can be calculated for average ponds, rivers and lakes using a reaeration rate ratio determined by Mabey et al. (1981), although the half-life may be significantly longer in deep bodies of water. Based on experimental data, the hydrolytic half-life of methyl bromide in water at 20-25°C can be calculated to be on the order of 20-38 days (Mabey and Mill, 1978; Castro and

Belser, 1981; Ehrenberg et al., 1974). Aquatic photolysis, oxidation, biodegradation, adsorption and bioaccumulation are not expected to be significant.

In the troposphere, the main route of methyl bromide degradation is reaction with hydroxyl radicals (Robbins, 1976); calculated half-lives are on the order of 0.5-1.0 year for typical atmospheres (see Table 2-2). At this decomposition rate, ~3% of the tropospheric methyl bromide is expected to diffuse eventually into the stratosphere (Callahan et al., 1979). Upon reaching the stratosphere, the methyl bromide is expected to undergo direct photolysis (Robbins, 1976); direct photolysis does not occur in the troposphere because methyl bromide does not absorb light >290 nm (Robbins, 1976).

Volatilization is the dominant fate mechanism for methyl bromide in soil (Sanborn et al., 1977; Jury et al., 1984; Brown and Rolston, 1980). Small amounts of methyl bromide are chemically transformed in soil with the amount of transformation to bromine ions increasing with an increase in soil organic content (Brown and Rolston, 1980). Significant leaching of methyl bromide has been demonstrated in greenhouse soils (Hegman et al., 1981; Vanachler et al., 1981) and in adsorption studies with various soil types (Daelmans and Siebering, 1977). Methyl bromide is considered a nonpersistent pesticide in soil (Sanborn et al., 1977).

3. EXPOSURE

3.1. WATER

Methyl bromide has been detected in various drinking waters (Kool et al., 1982), including water in Miami, FL (U.S. EPA, 1975) and three unidentified U.S. finished drinking waters (Shackelford and Keith, 1976). Greenberg et al. (1982) found methyl bromide in New Jersey groundwater.

In the preliminary findings of the U.S. EPA's National Urban Runoff Program (NURP), Cole et al. (1984) reported that methyl bromide was not detected in the stormwater runoff monitored in 15 U.S. cities.

Methyl bromide has been detected in seawater. Singh et al. (1977a) found methyl bromide concentrations of 0.14 ppb in shorewater from the California coast. The monitoring of seawater at 30 different global latitudes resulted in an average methyl bromide concentration of 1.2 ppb (Singh et al., 1983). At Kimmeridge, Dorset, England, methyl bromide concentrations of 2.5-6.5 ppb were tentatively identified in shorewater (Lovelock, 1975). The source of the methyl bromide in seawater is apparently natural formation (Singh et al., 1977b, 1983), although the mechanism for the formation is not clear.

In addition to the natural formation of methyl bromide in seawater, methyl bromide may also be exposed to surface waters by leaching of fumigated soils. Gould et al. (1983) tentatively identified methyl bromide in chlorinated landfill leachate and suggested that the methyl bromide is formed by the chlorination process; bromine, which is widely distributed in nature, is oxidized by hypochlorous acid to hypobromous acid, which is capable of forming haloorganic compounds. This may be a source of methyl bromide found in finished drinking water.

The gross analysis for methyl bromide from the U.S. EPA STORET Data Base reports 9082 water analyses with maximum and minimum concentrations of 202,662 $\mu\text{g/L}$ and 0 $\mu\text{g/L}$, respectively, with a median concentration of 67.5 $\mu\text{g/L}$. According to Staples et al. (1985), 1.4% of the STORET methyl bromide analyses are positive with the median concentration of positive analyses equal to <10 $\mu\text{g/L}$.

3.2. FOOD

Duggan et al. (1983) compiled the results of three Federal food monitoring programs: the Total Diet Study administered by the U.S. FDA; FDA's Monitoring Program for raw agricultural commodities, both domestic and imported and USDA's National Residue Program involving meat and poultry. Methyl bromide was found infrequently in leaf and stem vegetables with only three positive detections.

Residue studies have shown that methyl bromide disappears from fumigated foods within a few days, leaving only inorganic bromide residues for which the U.S. FDA establishes tolerances (Slenger, 1978).

3.3. INHALATION

Various air monitoring studies pertaining to methyl bromide are listed in Table 3-1. There appear to be several significant sources of methyl bromide exposure to the atmosphere. It is released directly into the atmosphere as a result of its use as a soil fumigant; indirect release is expected to occur from its use as a space fumigant (U.S. EPA, 1985). Based on monitoring studies, Harsch and Rasmussen (1977) have suggested that a significant source of methyl bromide in urban locations is the result of automobile exhaust (see Table 3-1). Catalytic decomposition of ethylene dibromide has been suggested as the methyl bromide source in auto exhaust (Singh et al., 1980). Turbine engines are also cited as a source of methyl

TABLE 3-1
Air Monitoring of Methyl Bromide

Concentration (ppt)	Location	Monitoring Dates	Remarks	Reference
30-52.8 ^a	Northern CA, shore	1975	none	Singh et al., 1977 ^a
100 ^a	Houston, TX	May 1980	none	Singh et al., 1982
81 ^a	St. Louis, MO	May-June 1980		
124 ^a	Denver, CO	June 1980		
259 ^a	Riverside, CA	July 1980		
84 ^a	Staten Is., NY	March-April 1981		
41 ^a	Pittsburgh, PA	April 1981		
47 ^a	Chicago, IL	April 1981		
5-20 ^a 5	Northern Hemisphere	Late 1977 High altitude	none May 1976	Singh et al., 1979
244 ^b	Los Angeles, CA	April 1979	none	Singh et al., 1981
67 ^b	Phoenix, AZ	April-May 1979		
55 ^b	Oakland, CA	June-July 1979		
16 ^a	Stanford Hills, CA	November 1975	none	Singh et al., 1977 ^a
93 ^a	Point Reyes, CA	December 1975		
108 ^a	Los Angeles, CA	May 1976		
24 ^a	Palm Springs, CA	May 1976		
5 ^a	Yosemite, CA	May 1976		
0-560 ^c	Southern CA coast	November 1982 to December 1983	none	Shikha et al., 1984
NR	Arkansas	NA	near manu- facturing sources	DeCarlo, 1979

TABLE 3-1 (cont.)

Concentration (ppt)	Location	Monitoring Dates	Remarks	Reference
<5	Rural Northwest U.S.	Dec. 1974-Feb. 1975	none	Grimsrud and Rasmussen, 1975
0.5-1.0 1000-55,000	Rural WA, air	1976	none leaded and unleaded gaso- line auto exhaust	Harsch and Rasmussen, 1977
185 10	NR NR	NR	heavy traffic light traffic	
14.4	Norway	Spring, 1983	none	Hov et al., 1984
9.1-14.7 ^d	Barrow, AL	1983	none	Rasmussen and Khalil, 1984
0.1-1.0	Stratosphere, 44°N	September 1980	none	Fabian et al., 1981
11	Arctic	March-April 1983	none	Berg et al., 1984

^a Average^b Mean^c Monthly mean^d Monthly average

NR = Not reported; NA = not applicable

bromide emissions (Graedel, 1978). The formation and release of methyl bromide from seawaters, however, may be the dominant source of atmospheric methyl bromide (Singh et al., 1983).

3.4. DERMAL

Although specific monitoring data could not be located in the available literature, the greatest source of methyl bromide exposure to the skin is likely to result from fumigant uses, particularly to occupational personnel.

3.5. SUMMARY

Methyl bromide has been detected in drinking water (Kool et al., 1982; U.S. EPA, 1975; Shackelford and Keith, 1976), groundwater (Greenberg et al., 1982), and seawater (Singh et al., 1977a, 1983; Lovelock, 1975). The presence of methyl bromide in seawater appears to be from natural formation (Singh et al., 1977a, 1983), and the release of methyl bromide from seawater to the atmosphere may be the dominant route of its atmospheric exposure (Singh et al., 1983). Water chlorination treatment is capable of forming bromo-organic compounds such as methyl bromide (Gould et al., 1983) and may contribute to the presence of methyl bromide in finished drinking waters. Although used as a fumigant for food products, methyl bromide disappears from fumigated foods within a few days, leaving only inorganic bromide residues (Slenger, 1978). Extensive monitoring of foods by Federal programs has resulted in infrequent detection of methyl bromide (Duggan et al., 1983). Atmospheric monitoring studies have detected methyl bromide in urban air, rural air, oceanic air, Arctic air, the stratosphere and near manufacturing plants (see Table 3-1). In addition to the atmospheric exposure resulting from seawater, methyl bromide is also emitted to the air as a result of fumigant uses (U.S. EPA, 1985) and automobile exhaust (Harsch and Rasmussen, 1977).

4. PHARMACOKINETICS

4.1. ABSORPTION

Rats treated orally with 250 $\mu\text{mol/kg}$ of ^{14}C -methyl bromide in corn oil excreted 36% of the administered radioactivity in the expired air and 43% in the urine (collected for 72 hours after dosing); 14% of the administered radioactivity was recovered in the carcass at 72 hours (Sections 4.2. and 4.4.) (Medinsky et al., 1984). These results indicate that at least 93% of the dose was absorbed by the gastrointestinal tract. The majority of the radioactivity, ~29% in expired air and ~38% in the urine, was excreted in the first 20 hours after dosing.

Methyl bromide is absorbed following inhalation exposure also. Groups of five male Fischer-344 rats were exposed to 50, 300, 5700 or 10,400 nmol/l (4.7, 28, 541 or 987 mg/m^3) of ^{14}C -methyl bromide by inhalation for 6 hours (Medinsky et al., 1985). Two rats in each group were killed after completing the exposure; the remaining three rats in each group were placed in metabolism cages. Analyses of the two rats killed immediately after treatment indicated that 48% of the inhaled methyl bromide was absorbed at the two lower concentrations, while 37 and 27%, respectively, were absorbed at the two higher concentrations. The first-order rate constant for methyl bromide absorption was 1.6 kg/hour for 6-hour exposure concentrations ≤ 5700 nmol/l (541 mg/m^3); however, the absorption rate for the highest concentration, 10,400 nmol/l (987 mg/m^3), was not linearly related to the lower concentrations. Noting that Gargas and Andersen (1982) determined a first-order rate constant of 0.32 kg/hour for 2-hour exposure concentrations of 197-924 ppm (765-3588 mg/m^3), Medinsky et al. (1985) speculated that the difference may be related partly to exposure duration. In light of a suggestion by Kornbrust and Bus (1983)

that glutathione conjugation may be a major metabolic pathway for methyl halides, Medinsky et al. (1985) conjectured that the rate-limiting factor on the absorption of methyl bromide at higher exposure concentrations may be the availability of glutathione.

Absorption of methyl bromide can be determined by measuring the amount of compound that disappears over time from a closed atmosphere inhalation chamber in which an animal is breathing (gas uptake method) or by measuring the amount of a stable metabolite within the animal's body, in this case, inorganic bromide (direct measurement methods). Gargas and Andersen (1982) compared these two methods of evaluating the absorption rate for methyl bromide. When groups of three male Fischer-344 rats were exposed to 100, 1000 or 3000 ppm (388, 3883, or 11,650 mg/m³) of methyl bromide for 175-205 minutes, the first-order rate constant for absorption determined by the gas uptake method was 0.55/kg hour. When groups of three male Fischer-344 rats were exposed to 197, 496 or 924 ppm (765, 1926 or 3588 mg/m³), presumably for a comparable length of time, the absorption rate determined by the direct measurement method followed a single rapid first-order process with a value of 0.32/kg hour.

4.2. DISTRIBUTION

Medinsky et al. (1984) reported that 72 hours after either oral or intraperitoneal administration of 250 μ mol of ¹⁴C-methyl bromide/kg bw to groups of three male Fischer 344 rats, 14 $\pm$ 2% of the administered radioactivity was recovered from the carcasses of rats treated orally, and 17 $\pm$ 6% of the administered radioactivity was recovered from the carcasses of rats treated by intraperitoneal injection. Of the tissues evaluated, including brain, spinal cord, skin, intestines and fat, the highest concentration of ¹⁴C-methyl bromide was found in the liver, followed by the kidney, testes,

lung, heart, stomach and spleen. There was no significant difference in the tissue concentration of methyl bromide that was due to route of administration except in the kidneys and stomach, which had a greater amount of residual radioactivity after oral administration of ^{14}C -methyl bromide.

In a subsequent study, Bond et al. (1985) exposed groups of three male Fischer-344 rats to 337 nmol/mL (32 mg/m³) ^{14}C -methyl bromide by inhalation. Rats were killed 0, 1, 2, 4, 8, 16, 24, 36, 48 and 65 hours following a single 6-hour exposure. Of the administered radioactivity, 27.0% was recovered from the carcasses of rats killed 65 hours after exposure. As indicated in Table 4-1 the highest concentration of radioactivity was found in the lungs, adrenals, kidneys, liver and turbinate bones immediately after exposure. The highest concentration of radioactivity 60 hours after exposure, however, was found in the liver, kidneys, stomach, thymus, lungs and adrenals. As indicated in Table 4-2, the longest half-life of radioactivity occurred in the liver (33.0 ± 4.9 hours), followed by the blood (7.7 ± 0.4 hours) and testes (6.2 ± 0.2 hours); whereas the shortest half-life occurred in the adrenals (1.6 ± 0.1 hours).

Medinsky et al. (1985) reported that the distribution of radioactivity in the carcasses of male Fischer-344 rats exposed to concentrations of 50, 300, 5700 or 10,400 nmol/L (4.7, 28, 541 or 987 mg/m³) of ^{14}C -methyl bromide for 6 hours was not dose-dependent (see Section 4.1.).

4.3. METABOLISM

By analogy to the metabolism of methyl chloride, as elucidated by Kornbrust and Bus (1983), Medinsky et al. (1985) suggested that methyl bromide reacts with sulfhydryl groups, in particular with the sulfhydryl group on glutathione in the liver, is then excreted in the bile as S-methylglutathione and subsequently reabsorbed in the small intestines. After reabsorption, methylglutathione is metabolized to a number of intermediates, such as

TABLE 4-1

Concentration (nmol/g) of ^{14}C in Tissues From Rats Exposed for 6 Hours
to 337 nmol [^{14}C]-Methyl Bromide/l Air^{a,b}

Tissue	0 Hour ^c	8 Hours	24 Hours	60 hours
Lung	250.4 $\pm$ 27.7 (3.6)	40.3 $\pm$ 5.5 (0.5)	19.5 $\pm$ 2.3 (0.2)	19.7 $\pm$ 2.3 (0.3)
Adrenal	242.0 $\pm$ 16.8 (11.9)	25.8 $\pm$ 10.2 (0.1)	23.0 $\pm$ 1.4 (0.0)	19.5 $\pm$ 3.4 (0.0)
Kidney	180.4 $\pm$ 4.6 (4.3)	76.1 $\pm$ 11.4 (1.5)	36.9 $\pm$ 2.6 (0.8)	35.1 $\pm$ 3.4 (0.7)
Liver	129.9 $\pm$ 7.0 (16.7)	119.6 $\pm$ 13.1 (11.6)	82.4 $\pm$ 10.3 (9.0)	37.8 $\pm$ 7.5 (3.9)
Turbinates	110.2 $\pm$ 6.5 (0.2)	35.2 $\pm$ 5.1 (0.1)	13.3 $\pm$ 1.4 (0.0)	18.9 $\pm$ 3.2 (0.0)
Spleen	98.6 $\pm$ 3.4 (0.7)	28.8 $\pm$ 5.8 (0.2)	15.9 $\pm$ 2.1 (0.1)	15.8 $\pm$ 1.7 (0.1)
Small Intestine	96.5 $\pm$ 14.6 (2.0)	36.3 $\pm$ 0.8 (0.4)	19.9 $\pm$ 1.8 (0.2)	15.5 $\pm$ 3.2 (0.2)
Trachea	84.3 $\pm$ 1.4 (0.1)	36.4 $\pm$ 6.3 (0.0)	15.5 $\pm$ 3.9 (0.0)	18.8 $\pm$ 4.3 (0.1)
Stomach	80.0 $\pm$ 1.8 (1.3)	37.8 $\pm$ 5.3 (0.6)	31.9 $\pm$ 1.0 (0.5)	27.0 $\pm$ 8.3 (0.4)
Large Intestine	66.3 $\pm$ 9.2 (0.9)	43.6 $\pm$ 8.6 (0.6)	19.0 $\pm$ 2.3 (0.1)	17.8 $\pm$ 2.3 (0.2)
Testes	65.4 $\pm$ 3.6 (2.5)	34.5 $\pm$ 3.9 (1.4)	17.1 $\pm$ 2.6 (0.6)	12.9 $\pm$ 2.3 (0.5)
Larynx	61.1 $\pm$ 4.9 (0.0)	27.1 $\pm$ 5.9 (0.0)	10.5 $\pm$ 1.2 (0.0)	11.6 $\pm$ 2.0 (0.0)
Brain	53.6 $\pm$ 9.5 (0.8)	35.8 $\pm$ 4.2 (0.6)	8.8 $\pm$ 1.1 (0.2)	7.4 $\pm$ 0.7 (0.1)

TABLE 4-1 (cont.)

Tissue	0 Hour ^c	8 Hours	24 Hours	60 hours
Heart	51.7±1.9 (0.6)	35.1±5.3 (0.4)	16.8±1.5 (0.2)	17.6±2.9 (0.2)
Thymus	48.4±0.5 (0.2)	33.3±6.7 (0.1)	19.9±2.3 (0.1)	23.4±3.1 (0.1)
Urinary bladder	45.6±6.9 (0.1)	27.7±5.5 (0.0)	12.6±1.9 (0.0)	11.8±1.4 (0.0)
Thyroid	28.7±24.4 (0.0)	34.8±6.1 (0.0)	16.1±2.6 (0.0)	16.4±1.4 (0.0)

^aSource: Bond et al., 1985

^bValues represent the $\bar{x} \pm$ SE of two to three rats. Values in parentheses are percentages of the absorbed [¹⁴C]-methyl bromide.

^cTime after end of exposure

TABLE 4-2

Half-Times for Disappearance of ^{14}C From Various Tissues of Rats
Exposed for 6 Hours to 337 nmol [^{14}C]-Methyl Bromide/l Air^{a,b}

Tissue	K_{el}^c (hour ⁻¹)	Half-time (hour)
Lung	-0.327	2.1 $\pm$ 0.04
Liver	-0.021	33.0 $\pm$ 4.9
Larynx	-0.163	4.3 $\pm$ 0.1
Nasal turbinates	-0.221	3.1 $\pm$ 0.1
Small intestine	-0.117	5.9 $\pm$ 0.3
Testes	-0.111	6.2 $\pm$ 0.2
Trachea	-0.188	3.7 $\pm$ 0.2
Kidneys	-0.167	4.1 $\pm$ 0.1
Adrenal	-0.434	1.6 $\pm$ 0.1
Brain	-0.125	5.5 $\pm$ 0.1
Blood	-0.090	7.7 $\pm$ 0.4

^aSource: Bond et al., 1985

^bEach point represents $\bar{x} \pm \text{SE}$ of two to three rats.

^cConcentration of ^{14}C in tissues (nmol/g) from individual rats were obtained. Data for all rats were pooled and expressed as concentration of ^{14}C in each tissue as a function of time after end of exposure. The data were fit to a nonlinear function by least-squares regression analysis. Half-times for disappearance of ^{14}C from tissues were determined from the equation $t_{1/2} = -0.693/K_{el}$, where K_{el} is the apparent rate constant for disappearance of ^{14}C obtained from regression analysis. The equation used to fit the data was $F(t) = Ae^{kt} + B$, where $F(t)$ is the fraction remaining to be excreted in time t (hr) and A is the fraction excreted with an apparent rate constant of k , and B is a constant.

N-acetyl-S-methylcysteine or methylthioacetic sulfoxide, which are excreted in the urine or to S-methylcysteine, which is further metabolized to formate with subsequent production of CO_2 (Kornbrust and Bus, 1983; Medinsky et al., 1985).

4.4. EXCRETION

In order to compare the excretion of methyl bromide after oral and intraperitoneal administration, one group of three Fischer-344 rats was given a single oral dose of 250 μmol ^{14}C -methyl bromide/kg bw in 0.5 ml of corn oil (Medinsky et al., 1984). Another group of three Fischer-344 rats was given a single intraperitoneal injection of 250 μmol ^{14}C -methyl bromide/kg bw in corn oil. A third group of three male Fischer-344 rats received a glass bile cannula inserted surgically under light halothane anesthesia and was treated 1 hour postoperatively with a single oral dose of 180 μmol ^{14}C -methyl bromide/kg bw in 0.5 ml of corn oil. The rats were placed in metabolism cages immediately after dosing. The urine and feces were collected at 4, 7, 10, 16, 20, 35, 32, 48, 54 and 72 hours after treatment. In addition, the expired air was collected and analyzed. During the 72 hours after oral administration of ^{14}C -methyl bromide, 32% of the administered radioactivity was recovered as CO_2 and 4% as methyl bromide from the expired air, 43% from the urine and <3% from the feces. Excretion in the expired air and urine was biphasic with ~29 and 38%, respectively, excreted in the first 20 hours. During the 72 hours after intraperitoneal injection of ^{14}C -methyl bromide, 45% of the administered radioactivity was recovered as CO_2 and 20% as methyl bromide from the expired air, 16% from the urine and <3% from the feces. During the 24 hours after oral administration of ^{14}C -methyl bromide to the rats with the bile cannula, 46% of the administered dose was recovered from the bile.

The half-life for biliary excretion of methyl bromide was ~4 hours. Bile collection prevented enterohepatic recirculation, and consequently, significantly decreased the amount of radioactivity excreted by the lungs and kidneys.

In order to evaluate the excretion of methyl bromide after inhalation exposure, one group of four male Fischer-344 rats was exposed to 337 nmol/l (32 mg/m³) of ¹⁴C-methyl bromide for 6 hours (Bond et al., 1985). The urine and feces were collected at 4, 7, 10, 16, 20, 24, 42 and 65 hours after the end of the treatment. In addition, the expired air was collected and analyzed. During the 65 hours after inhalation exposure, 46.7% of the administered radioactivity was recovered as CO₂ and 1.0% as methyl bromide from the expired air, 22.7% from the urine and 2.0% from the feces. The half-lives for excretion of ¹⁴C in the urine and feces were monophasic with values of 9.6 and 16.1 hours, respectively. The half-life for excretion of ¹⁴C by the lungs was biphasic with values of 3.9 and 11.4 hours for the α and β phases, respectively.

Groups of five male Fischer-344 rats were exposed to 50, 300, 5700 or 10,400 nmol/l ¹⁴C-methyl bromide of air (4.7-987 mg/m³) for 6 hours (Medinsky et al., 1985). Two of the rats in each group were killed immediately after completing the treatment for use in absorption studies (see Section 4.1.). The remaining three rats from each group were placed in metabolism cages and the urine and feces collected 4, 7, 12, 16, 20, 24, 40, 48 and 66 hours after the treatment. In addition, the expired air was collected and analyzed. The distribution and excretion rates of methyl bromide were independent of the amount absorbed. Urinary excretion of radioactivity appeared to follow first-order kinetics with a half-life of

9.9 hours. Elimination of ^{14}C by the lungs appeared to follow second-order kinetics with half-times of 4.1 and 17 hours for the α and β phases, respectively.

4.5. SUMMARY

Methyl bromide was absorbed following oral (Medinsky et al., 1984) and inhalation (Medinsky et al., 1985; Gargas and Andersen, 1982; Bond et al., 1985) exposure of rats. If an orally administered dose, at least 93% was absorbed (Medinsky et al., 1984). At low inhalation exposure levels ($<540 \text{ mg/m}^3$) for 6 hours, ~50% of the inhaled methyl bromide was absorbed, and absorption followed first-order kinetics (Medinsky et al., 1985). At a higher exposure level (987 mg/m^3), methyl bromide absorption followed second-order kinetics. Noting that glutathione conjugation may be a major metabolic pathway for methyl halides (Kornbrust and Bus, 1983), Medinsky et al. (1985) suggested that absorption may depend upon duration of exposure and that the rate-limiting factor may be the availability of glutathione. Especially, since according to Gargas and Andersen (1982), transpulmonary absorption followed first-order kinetics at high exposure levels ($765\text{--}3588 \text{ mg/m}^3$ for 2 hours). The highest relative concentrations of ^{14}C -methyl bromide occurred in the lungs, kidneys, liver and stomach after either oral or inhalation exposure (Medinsky et al., 1984; Bond et al., 1985). The liver contained the highest concentration of ^{14}C -methyl bromide after oral exposure (Medinsky et al., 1984), whereas the lungs contained the highest concentration of ^{14}C -methyl bromide after inhalation exposure (Bond et al., 1985). The longest half-life of ^{14}C -methyl bromide occurred in the liver, followed by the blood and the testes after inhalation exposure (Bond et al., 1985). Methyl bromide may react with sulfhydryl groups and therefore with glutathione (Medinsky et al., 1984). Biliary excretion of

S-methylglutathione is followed by reabsorption of S-methylglutathione and metabolizes further to substances eliminated by the lungs or kidneys. Collection of bile during the 24 hours following oral dosing of rats resulted in the recovery of 46% of the administered radioactivity (Medinsky et al., 1984). Urinary excretion of ^{14}C -methyl bromide metabolites was the main route of elimination after oral administration, whereas pulmonary excretion was the main route of elimination after inhalation exposure (Medinsky et al., 1984; Bond et al., 1985). Following oral dosing, excretion in the urine and expired air was biphasic. Following inhalation exposure, urinary excretion followed first order kinetics, but pulmonary excretion followed second-order kinetics (Medinsky et al., 1985; Bond et al., 1985).

5. EFFECTS

5.1. CARCINOGENICITY

The National Toxicology Program is testing methyl bromide in rats and mice by inhalation exposure, and the preliminary subchronic studies are in progress (NTP, 1985).

Groups of 10 male and 10 female Wistar rats were treated by gavage with 0, 0.4, 2, 10 or 50 mg/kg/day of methyl bromide dissolved in arachis oil, 5 days/week for 13 weeks (Danse et al., 1984). At the end of the treatment period, neoplastic and hyperplastic lesions were not significantly increased in the forestomachs of the control rats or the rats treated with 0.4 or 2 mg/kg/day of methyl bromide. In the 50 mg/kg/day group, six females and seven males treated with methyl bromide had carcinoma of the forestomach. Advanced diffuse hyperplasia of the stratified squamous epithelium in the forestomach was reported to have occurred in 8 female and 10 male rats treated with 50 mg/kg/day of methyl bromide. Slight but diffuse hyperplasia of the stratified squamous epithelium in the forestomach was reported in nine female and six male rats treated with 10 mg/kg/day of methyl bromide. No additional histopathology was observed in the liver or spleen from all groups, in the esophagus from the control and high-dose group or in the lungs from the two highest dose groups. The incidence of slight atelectasis was increased over controls in both male (4/10) and female (5/10) rats treated with 50 mg/kg/day.

Although there was a dose-dependent increase in hyperplasia, tumors were reported only at the highest dose tested. According to the U.S. EPA (1984a, 1985), however, the NTP scientists who reevaluated the histological slides from the Danse et al. (1984) study concluded that there were no neoplastic lesions in the forestomachs of rats treated with 50 mg/kg/day of methyl bromide, only hyperplastic lesions and inflammation.

An epidemiology study indicated that the incidence of testicular cancer was significantly higher than expected in a group of workers exposed to organic bromides (Wong et al., 1984) (see Section 5.5.). Two men out of a group of 665 workers exposed to organic bromides, with the only common potential exposure being methyl bromide, developed testicular cancer (Table 5-1). The expected number of testicular cancer cases in a group of 665 was reported to be 0.11. A significantly increased incidence of any other type of tumor was not observed in this study.

5.2. MUTAGENICITY

As indicated in Table 5-2, methyl bromide was mutagenic to Salmonella typhimurium strains TA100 and TA1535, but not to strains TA98 and TA1537, regardless of metabolic activation (Voogd et al., 1982; Moriya et al., 1983; Kramers et al., 1985). In a number of studies (Simmon and Tardiff, 1977; Simmon, 1978, 1981; Simmon et al., 1977), methyl bromide was observed to be mutagenic to S. typhimurium strain TA100 in the absence of metabolic activation when evaluated with the desiccator assay. Methyl bromide was more mutagenic than methyl chloride (Simmon, 1981). Methyl bromide was mutagenic to Escherichia coli regardless of metabolic activation (Moriya et al., 1983; Djalali-Behzad et al., 1981). The mutagenicity of methyl bromide in bacteria is consistent with its alkylating properties (Djalali-Behzad et al., 1981) in that it is a direct-acting mutagen that induces primarily base-pair mutations.

In addition to methyl bromide being a bacterial mutagen, it is reported to be mutagenic in eukaryotic organisms. Methyl bromide was reported to cause sex-linked recessive lethals in Drosophila melanogaster (Voogd et al., 1982; Kramer et al., 1985; McGregor, 1981; Katz, 1985; Kramers and Bissumbhar, 1983). Also, methyl bromide has been shown to induce gene mutations at two different loci in the mouse lymphoma cell L5178Y assay (Table 5-3).

TABLE 5-1

Increased Incidence of Testicular Tumors in Male Workers Exposed to Organic Bromides (Methyl Bromide)^{a,b}

Exposure Route	Size of Exposed Population	Size of Control Population	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	SMR (p value)
Occupational, presumably inhalation	665	U.S. white male mortality rates	41 years (3579 person-years)	testes	cancer	2	0.11	1799 (<0.05)

QUALITY OF EVIDENCE

Weakness of Study: multiple chemical exposure; uncontrolled exposure levels

Overall Adequacy: limited

^aSource: Wong et al., 1984^b Level of exposure was not reported.

TABLE 5-2
Bacterial and *Drosophila* Mutagenicity Testing of Methyl Bromide

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System (S9)	Response	Comment	Reference
Gene reversion	<i>Salmonella</i> <i>typhimurium</i> TA100	plate test in air	≥ 1.9 g/m ³	-	+	abstract	Voogd et al., 1982
Gene reversion	<i>S. typhimurium</i> TA100	in medium	≥ 285 mg/kg	-	+	abstract	Voogd et al., 1982
Gene reversion	<i>S. typhimurium</i> TA100, TA1535 TA98, TA1537	plate overlaid with gas	≤ 50 g/m ³	+/	+/	MC	Moriya et al., 1983
		plate overlaid with gas	≤ 50 g/m ³	+/	-/-	MC	Moriya et al., 1983
Gene reversion	<i>S. typhimurium</i> TA100	in air	0-0.2%	-	+	MC	Simon and Tardiff, 1978
Gene reversion	<i>S. typhimurium</i> TA98 TA100	plate overlaid with gas	$0-5 \times 10^{-6}$ mg/m ³	+/	-/-	MC	Kramers et al., 1985
		plate overlaid with gas	$0-5 \times 10^{-6}$ mg/m ³	+/	+/	MC	Kramers et al., 1985
Gene reversion	<i>Klebsiella</i> <i>pneumoniae</i>	in air	$4.75-19.0$ g/m ³	-	+	MC	Voogd et al., 1982
Gene reversion	<i>E. coli</i> WP2 hcr	plate overlaid with gas	~ 50 g/m ³	+/	+/	MC	Moriya et al., 1983
Forward mutation	<i>E. coli</i> Sd-4		0-7 mM/hr		low	MC	Djalali-Behzad et al., 1981
Fluctuation test	<i>Klebsiella</i> <i>pneumoniae</i> ur-pro-	in air	$0-19 \times 10^{-6}$ mg/m ³	-	+	MC	Kramers et al., 1985
Lethal recessive	<i>D. melanogaster</i>	in air	375 mg/m ³ for 30 hours 200 mg/m ³ for 90 hours	NA	+	MC	Voogd et al., 1982
Lethal recessive	<i>D. melanogaster</i>	in air	0, 20 to 70 ppm for 5 hours	NA	-	the results were neither dose-related nor repeatable	McGregor, 1981
Lethal recessive	<i>D. melanogaster</i>	in air	70-750 mg/m ³ , 6 hours/day, 1-3 weeks	NA	+	MC	Kramers et al., 1985

NA = Not applicable; MC = no comment

TABLE 5-3
Mutagenicity Testing of Methyl Bromide in Mammalian Systems

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System (S9)	Response	Comment	Reference
Unscheduled DNA synthesis	human diploid fibroblasts	In air	<70% for 3 hours	+/-	-/-	NC	McGregor, 1981
Unscheduled DNA synthesis	rat primary liver	In the culture medium	10 and 30 mg/kg	NA	-	NC	Voogd et al., 1982
Unscheduled DNA synthesis	male Wistar rat liver cells- primary culture	In the culture medium	4 mg/ml in ethanol	NA	-	NC	Kramers et al., 1985
Viral enhanced cell trans- formation	hamster embryo cells	In the culture medium	0, 1, 2, 4 or 8 ppt	NR	-	NC	Hatch et al., 1983
Forward mutation	mouse L5178Y lymphoma cells	In the culture medium	>0.3 mg/kg	NR	+	NC	Voogd et al., 1982
Forward mutation	mouse L5178Y lymphoma cells	In the culture medium	0-3 mg/kg	NR	+	Mutation was seen at concentration of 10 ⁻⁵ mg/kg; at concentrations >0.3 mg/kg decreased cell survival was reported	Voogd et al., 1982
Dominant lethal	male Sprague- Dawley rats	Inhalation	0, 20 or 70 ppm 7 hours/day for 5 days	NA	-	NC	McGregor, 1981
Chromosome abnormality (bone marrow cells)	male and female CD Sprague- Dawley rats	Inhalation	0, 20 or 70 ppm 7 hours/day for 5 days	NA	-	NC	McGregor, 1981
Sperm abnormality	male B6C3F1 mice	Inhalation	0, 20 or 70 ppm 7 hours/day for 5 days	NA	-	NC	McGregor, 1981

NR = Not reported; NC = no comment; NA = not applicable

Methyl bromide does not appear to elicit unscheduled DNA synthesis (UDS) in rat liver cells (Voogd et al., 1982; Kramers et al., 1985) or human fibroblasts (McGregor, 1981). However, certain kinds of DNA lesions that lead to mutations may not stimulate the repair process or do so to such a small extent that UDS would not be detectable by available methods. In vivo chromosomal aberration tests in rats and the sperm morphology tests in mice were negative (McGregor, 1981).

5.3. TERATOGENICITY

New Zealand White rabbits were artificially inseminated and groups of ~20 pregnant females were exposed by inhalation to 0, 20 or 70 ppm (0, 78 or 272 mg/m³) of methyl bromide for 7 hours/day, 5 days/week (Hardin et al., 1981; Sikov et al., 1980). The rabbits were killed on day 30 of gestation. In the 70 ppm exposure group, methyl bromide was highly toxic, resulting in convulsive movements, hindleg paresis and death, beginning on day 9 of gestation. Because of the observed toxicity, exposure in all groups was discontinued on day 15 of gestation. Nonetheless, all but one of the pregnant rabbits in the group exposed to 70 ppm of methyl bromide died by day 30 of gestation. No evidence of maternal toxicity or fetal teratogenicity was observed in the group exposed to 20 ppm of methyl bromide. Despite the signs of toxicity among rabbits exposed to 70 ppm methyl bromide, no teratogenic or fetotoxic effects were observed in their fetuses. The number of resorptions appears to be greater among rabbits exposed to 20 ppm of methyl bromide during gestation than among controls (Table 5-4). Although not statistically significant at the low-dose level, the resorption rate at the high dose was not significant because all but one of the rabbits died.

Female Wistar rats were divided into seven groups of ~35 rats each (Hardin et al., 1981; Sikov et al., 1980). Two groups were treated by

TABLE 5-4

Fecundity, Embryotoxicity and Fetal Viability in Pregnant Rabbits
Exposed to Methyl Bromide or Filtered Air from Day 1-24 of Gestation^a
(Results are expressed as mean $\pm$ S.D., except as noted)

Measure	Gestational Exposure Level		
	Air	Low	High
Number of litters	17	13	1
Corpora lutea/doe	9.3 $\pm$ 2.0	9.6 $\pm$ 3.0	11.0
Number of implants/litter	8.3 $\pm$ 2.5	8.0 $\pm$ 3.4	8.0
Implants/corpus luteum	0.89 $\pm$ 0.20	0.77 $\pm$ 0.26	0.73
Number live fetuses	128	85	8
Number dead fetuses	0	2	0
Number of resorptions	13	17 ^b	0
Live fetuses/litter	7.5 $\pm$ 2.6	6.5 $\pm$ 3.8	8.0
Dead fetuses/litter	0.0 $\pm$ 0.0	0.15 $\pm$ 0.56	0.0
Resorptions/litter	0.71 $\pm$ 1.5	1.3 $\pm$ 3.3	0.0
% Early ^c	3.6	13.5	0.0
% Mid ^c	1.4	1.0	0.0
% Late ^c	2.9	1.9	0.0
Total%	7.9	16.4	0.0
Number of litters with resorptions	7	6	0
% Litters with resorptions	41.2	46.2	0.0
Resorptions/litters with resorptions	1.9 $\pm$ 1.9	2.8 $\pm$ 4.5	0.0

^aSource: Sikov et al., 1980

^bTwelve of the 17 occurred in one litter, which was completely resorbed; one litter consisted of a single resorption site.

^cCalculated as percent of total implants

inhalation with 20 ppm (78 mg/m³) and two groups were treated with 70 ppm (272 mg/m³) of methyl bromide for 7 hours/day, 5 days/week for 3 weeks before mating to simulate occupational exposure. The remaining three groups were exposed to air only. After mating, the respective groups of rats were exposed to 0, 20 or 70 ppm of methyl bromide for 7 hours/day on days 1-19 of gestation in such a way as to provide seven different treatment groups consisting of air-air, air-low, air-high, low-low, low-high, high-low and high-high exposed rats. As indicated in Table 5-5, the only effect was a decreased number of resorptions observed in the rats exposed to 70 ppm of methyl bromide during gestation. There was no evidence of maternal toxicity, teratogenicity or fetal toxicity in the rats at any exposure level.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of methyl bromide could not be located in the available literature as cited in the Appendix. According to U.S. EPA (1985), a 2-generation reproduction study performed for Great Lakes Chemical Corporation is in progress.

5.5. SUBCHRONIC AND CHRONIC TOXICITY

As discussed in Section 5.1., groups of 10 male and 10 female Wistar rats were treated by gavage with 0, 0.4, 2, 10 or 50 mg/kg/day of methyl bromide dissolved in arachis oil, 5 days/week for 13 weeks (Danse et al., 1984). There was a significantly decreased body weight gain among male rats treated with 50 mg/kg/day of methyl bromide. Throughout the study, food consumption was significantly lower than that of the control groups in both males and females treated with 50 mg/kg/day of methyl bromide, and slightly but significantly lower after 9 weeks in the males treated with 2 mg/kg/day of methyl bromide and after 6 and 9 weeks in males treated with 10 mg/kg/day of methyl bromide.

TABLE 5-5

Fecundity, Embryotoxicity and Fetal Viability in Pregnant Rats Exposed Pregestationally and Gestationally to Methyl Bromide and/or Filtered Air^a
(Results are expressed as mean $\pm$ S.D., except as noted)

Measure	Pregestational-Gestational Exposure Level					
	Air-Air	Air-Low	Air-High	Low-Air	Low-Low	High-High
Number of litters	37	31	36	34	38	36
Corpus lutea/dam	14.9 $\pm$ 2.7	14.0 $\pm$ 2.3	15.0 $\pm$ 2.8	14.9 $\pm$ 2.6	16.4 $\pm$ 3.4	14.5 $\pm$ 2.6
Number of implants/litter	12.2 $\pm$ 3.0	12.7 $\pm$ 2.1	12.9 $\pm$ 1.6	13.3 $\pm$ 2.3	13.4 $\pm$ 3.0	13.3 $\pm$ 2.1
Implants/corpus luteum	0.83 $\pm$ 0.22	0.93 $\pm$ 0.18	0.88 $\pm$ 0.14	0.90 $\pm$ 0.14	0.83 $\pm$ 0.19	0.92 $\pm$ 0.11
Number live fetuses	427	379	456	430	484	466
Number dead fetuses	1	0	0	1	0	0
Number of resorptions	24	16	8	20	25	8
Live fetuses/litter ^b	11.5 $\pm$ 3.2	12.2 $\pm$ 2.4	12.8 $\pm$ 1.6	12.7 $\pm$ 2	12.7 $\pm$ 2.8	12.9 $\pm$ 2.1
Dead fetuses/litter	0.03 $\pm$ 0.16	0.0	0.0	0.3 $\pm$ 0.17	0.0	0.0
Resorptions/litter ^b	0.65 $\pm$ 1.4	0.52 $\pm$ 0.93	0.22 $\pm$ 0.42	0.56 $\pm$ 0.75	0.63 $\pm$ 1.2	0.33 $\pm$ 0.54
% Early ^c	3.8	2.8	1.1	3.1	3.0	1.7
% Mid ^c	1.5	1.3	0.43	0.89	1.6	0.63
% Late ^c	0.0	0.0	0.22	0.22	0.20	0.0
Total ^c	5.3	4.1	1.6	4.2	4.8	2.3
Number of litters with resorptions	14	10	8	14	13	6
% Litters with resorptions	37.8	32.3	22.2	41.2	34.2	30.6
Resorptions/litters with resorptions	1.7 $\pm$ 1.9	1.6 $\pm$ 1.0	1.0 $\pm$ 0.0	1.4 $\pm$ 0.50	1.9 $\pm$ 1.4	1.1 $\pm$ 0.30
						1.3 $\pm$ 0.52

^aSource: Sikov et al., 1980

^bDenotes statistically significant ($p \leq 0.05$) differences in group variances for indicated measure.

^cCalculated as percent of total implants

Male rats treated with 50 mg/kg/day of methyl bromide had a slight but significant decrease ($p < 0.05$) in the red blood cell count, accompanied by a slight but significant elevation ($p < 0.05$) in mean corpuscular volume. The white blood cell count was significantly increased ($p < 0.01$) in female but not male rats treated with 50 mg/kg/day of methyl bromide. Differential white counts indicated that the number of lymphocytes increased ($p < 0.05$) in the females treated with 50 mg/kg/day of methyl bromide and the number of neutrophils increased ($p < 0.05$) in the males treated with 50 mg/kg/day of methyl bromide. The clinical significance of these changes is not apparent. Dose-related increased incidence and severity of hyperplasia of the forestomach occurred at 10 and 50 mg/kg/day. The increased incidence of atelectasis observed in both males and females in the high-dose groups may have been due to inhaled methyl bromide during gavage. Evaluation of liver histology apparently did not reveal any treatment related effects. The renal histology was not evaluated. Danse et al. (1984) concluded that the changes in body weight, hematology and histology observed in the rats treated with methyl bromide were secondary to the forestomach lesions.

Beagle dogs of either sex were fed methyl bromide fumigated food ad libitum so that groups of four dogs each ingested ~35, 75 or 150 mg/kg/day of bromide, or adjusting for molecular weight, 41.6, 89.1 or 178.2 mg/kg/day of methyl bromide, assuming all the bromide was present as methyl bromide, for 1 year (Rosenblum et al., 1960). The control group consisted of three male and three female dogs fed only dog chow, ad libitum. The dogs ingesting 178.2 mg/kg/day methyl bromide gained more weight than the controls or the two lower treatment groups. The dogs in the high-dose group also became lethargic and displayed excessive salivation and diarrhea occasionally.

Methyl bromide was reported to have no effect on hematological values, urinalysis, blood chemistry (including BUN levels) or mortality rate. Mild chronic renal inflammation was reported in two dogs in the high-dose group and in one dog in the control group. Mild hepatic focal inflammation was reported in three dogs in the high-dose group, two dogs in the low-dose group and one dog in the control group. No other histological lesions were reported.

Groups of male and female rats, guinea pigs, rabbits and monkeys were exposed by inhalation to several levels of methyl bromide for 7.5-8 hours/day, 5 days/week for up to 6 months (Irish et al., 1940). The number of animals in each group and the level of exposure are summarized in Table 5-6.

In the rats, all died after three or four exposures to 0.85 mg/l (219 ppm) of methyl bromide. Convulsions occurred in 7/30 rats exposed to 0.42 mg/l (108 ppm) of methyl bromide, as well as weight loss in 9 rats and histopathological changes in the lungs of ~20 rats. No further histological effects were reported. No adverse effects were reported in rats at ≤ 0.25 mg/l (≤ 64 ppm).

In the guinea pigs, histological alteration of the lungs (characterized by congestion, edema and leukocytic infiltration) accompanied by hemorrhaging occurred in most of the 14 guinea pigs that died after one to three exposures to 0.85 mg/l (219 ppm) of methyl bromide. Although 4/11 guinea pigs exposed to 0.42 mg/l (108 ppm) of methyl bromide died, histological examination revealed no alteration in the liver, kidney, spleen, pancreas or adrenal in any of the 8/11 guinea pigs examined. Less severe pulmonary alterations were observed in the lungs of guinea pigs exposed to 0.42 mg/l (108 ppm) than in the lungs of guinea pigs exposed to 0.85 mg/l (219 ppm). No adverse effects were observed in guinea pigs exposed to 0.13 or 0.25 mg/l (34 or 64 ppm) of methyl bromide.

TABLE 5-6

Summary of Experimental Design of Irish et al., 1940 Study

Exposure Level		Number of Animals			
(mg/L)	(ppm)	Rats	Guinea pigs	Rabbits	Monkeys
0	0	15	6 males; 6 females	6	2
0.065	17	0	0	6	0
0.13	34	8 males; 8 females	5 males; 6 females	58	4
0.25	64	10 males; 12 females	14 males; 10 females	42	6
0.42	108	30	11	0	1 female
0.85	219	20	16	0	0

In the rabbits exposed to 0.25 mg/l (64 ppm), all died or were killed while moribund, and 28/42 became severely paralyzed either in the fore or hind quarters. At the 0.13 mg/l (34 ppm) dose level, 34/58 rabbits developed paralysis. Some of the rabbits in this treatment group died from a severe lung infection that occurred before signs of paralysis developed. Among the 24/58 rabbits that did become paralyzed, there was a high incidence of pulmonary damage. Paralysis was not observed in any of the six rabbits in the control group or in the group of six rabbits exposed to 0.065 mg/l (17 ppm) of methyl bromide. Histological evaluation of the livers, kidneys and brains of rabbits with paralyzed limbs revealed no treatment-related effects.

The one monkey exposed to 0.42 mg/l (108 ppm) of methyl bromide experienced severe convulsions after 2 weeks of treatment. Of monkeys exposed to 0.25 mg/l (64 ppm) of methyl bromide, 3/6 became paralyzed, one of which had convulsions. The four monkeys exposed to 0.13 mg/l (34 ppm) of methyl bromide appeared not to have adverse effects. There were no hematological effects from methyl bromide treatment. Histological evaluation of the monkeys was not reported.

Six adult male New Zealand White rabbits were exposed to 27 ppm (105 mg/m³) methyl bromide by inhalation, 7.5 hours/day, 4 days/week during an 8-month period for a total duration of 900 hours (Russo et al., 1984). Two adult male New Zealand White rabbits served as the control group. No effects from methyl bromide exposure on the mean latency rates of the sciatic and ulnar nerves or on eyeblink amplitudes were observed. The rabbits exposed to methyl bromide gained less weight than the two control rabbits, but this difference was reported to be unrelated to treatment. In reference to the earlier finding of Irish et al. (1940) that an exposure

concentration of 34 ppm (0.13 mg/l or 130 mg/m³) for 7.5 hours/day, 5 days/week methyl bromide caused paralysis in 34/58 rabbits. Russo et al. (1984) conjectured that their failure to find neurobehavior impaired in rabbits exposed to concentrations of 27 ppm (105 mg/m³) methyl bromide may have been due to the differences in the strain of the rabbits, to the possibility that the range of 27-33 ppm of methyl bromide defines the threshold level for the incidence of neurobehavioral impairment as a result of exposure, or more likely [since Irish et al. (1940) did not report the details of their analytical procedures] to imprecise monitoring procedures that resulted in variations of concentrations which influenced the effects of exposure. Furthermore, Irish et al (1940) exposed the rabbits 5 days/week, while Russo et al. (1984) exposed them for 4 days/week (34 ppm x 5/7 = 24 ppm; 27 ppm x 4/7 = 15 ppm).

One group of 32 Sprague-Dawley rats (sex not specified) was exposed to 55 ppm (214 mg/m³) of methyl bromide 5 days/week, 6 hours/day for 36 weeks over a 12-month period (Anger et al., 1981). Eight Sprague-Dawley rats (sex not specified) served as the control group. No additional information regarding the dosing schedule was reported. No significant difference between treated and control groups was observed in body weight, in grip-coordination, in activity as measured by a typical open field apparatus or in mean conduction velocity in the sciatic or ulnar nerves. No other parameters were reported.

Although the abstracts of a series of a Japanese studies (Shibata et al., 1979; Yomura and Shibata, 1979) reported decreased body weight gain, discoloration of hair and skin, periorcular discoloration, diarrhea, excitation, adynamia, softening of abdominal wall, postural and gait disturbances, degeneration of peripheral nerves and the posterior columns in the spinal

cord and mild hepatic lesions in young female Wistar rats fed methyl bromide fumigated food for 45 weeks, it was not possible to determine the concentration in food or the ingested dose of methyl bromide. A translation of these studies by Nakatsugawa (1985) revealed that the methyl bromide apparently dissipated from the fumigated pellets, because analysis with a detection limit of 5-10 ppm revealed no methyl bromide and no difference in organic bromine content between fumigated and control diets.

An epidemiology study evaluating the health effects of brominated compounds including 1,2-dibromo-3-chloropropane, 2,3-dibromopropyl phosphate, poly brominated biphenyls, organic and inorganic bromides and DDT on 3579 male chemical workers employed between 1935 and 1976 indicated that the incidence of digestive system cancers and diseases, cirrhosis of the liver and diseases of the circulatory system were significantly less than expected (Wong et al., 1984). The incidence of deaths from diabetes mellitus was the only disease that occurred more frequently than expected in men exposed to brominated compounds. Of the entire cohort, 665 workers were exposed to organic bromide. A significant increase ($p < 0.05$) in the incidence of testicular cancer was observed (two deaths observed, 0.11 expected). The standardized mortality ratio was the comparison statistic used. The only chemical that both men were occupationally exposed to was methyl bromide.

The blood bromine and transaminase levels and EEGs in a group of men (ages 21-63 years; median, 32 years) in the Netherlands occupationally exposed to methyl bromide for time periods ranging from a few months to 11 years (median, 2 years) were evaluated by Verberk et al. (1979). The blood bromide levels of the workers ranged from 4-23 ppm. The blood bromide levels of pooled, presumably unexposed, whole human blood was found to be 3.7 ppm by DeGaeij et al. (1976). Although the levels of transaminases in

the blood of workers exposed to methyl bromide were not significantly increased compared with accepted norms, there was a significant correlation between increased bromide levels and increased transaminase levels. The EEG was abnormal in 10 of the workers examined, and workers with abnormal EEGs had higher blood bromide levels. No correlation between blood bromide levels and neurological signs, such as hyporeflexia, myoclonia, ataxia or nystagmus was observed. Verberk et al. (1979) concluded that workers with blood bromide levels >12 ppm have 3.5 times the probability of an abnormal EEG reading than workers with blood bromide levels ≤ 12 ppm.

Chronic human exposure is difficult to quantify because methyl bromide appears to be toxic at least to some individuals at levels that do not produce irritating olfactory or general sensations. Neurological/psychological symptoms are usually the reason that an individual exposed to methyl bromide must seek medical assistance (Zatuchni and Hong, 1981; Chavez et al., 1985). A 19-year-old male fumigator exposed to methyl bromide for 10 months and then an additional 2 months after a 6-month hiatus, had neurological symptoms including headache, weakness and abdominal pain several weeks before admission for psychiatric treatment (Zatuchni and Hong, 1981). Neurological symptoms encountered during the disease included difficulty in walking and speaking and alterations in the EEG. In another report, a 32-year-old male fumigator suffered permanent optic nerve damage after several years of working with methyl bromide (Chavez et al., 1985). In addition to adverse effects on vision, he had elevated serum bromide levels, difficulty breathing, headaches, burning sensations in the extremities, and weakness.

The English abstract of a Russian study (Shapovalov, 1974) reported that there was moderate hypoglycemia, hypercholesterolemia, decreased bilirubin levels and thyroid changes in 140 workers who were continuously exposed to elemental bromide and methyl bromide.

5.6. OTHER RELEVANT INFORMATION

Danse et al. (1984) estimated 214 mg/kg bw to be an oral LD₅₀ for rats. In a series of experiments with rats and rabbits, Irish et al. (1940) defined the exposure concentration and duration that resulted in 100% mortality and 100% survival. In rats, exposure to 50 mg/l (12,865 ppm) was 100% lethal after 6 minutes, but 100% of the rats survived if exposed for <3 minutes; exposure to 1 mg/l (257 ppm) was 100% lethal after 22 hours, but 100% of the rats survived if exposed for <8 hours. In rabbits, exposure to 50 mg/l (12,865 ppm) was 100% lethal after 30 minutes, but 100% of the rabbits survived if exposed for <12 minutes; exposure to 1 mg/l was 100% lethal after 24 hours, but 100% of the rabbits survived if exposed for <15 minutes. Neurological effects, such as hunching, drowsiness, excitability, lacrimation, paralysis, changes in pulmonary histology and kidney changes (not specified) were reported after acute exposure (Irish et al., 1940). Alexeeff (1983) reported that the LC₅₀ for mice exposed to methyl bromide for 1 hour was 4.5 mg/l (1158 ppm) and emphasized the steep dose-response curve.

As summarized in U.S. EPA (1981), fatal human poisoning has occurred after acute exposure to 1164-1552 mg/m³ (300-400 ppm) of methyl bromide. The primary targets of methyl bromide in humans are the nervous system and the gastrointestinal system. Pulmonary edema may result in death within hours after methyl bromide exposure, whereas circulatory failure is the precipitating cause of death if a victim survives longer. Degenerative changes are also seen in the kidneys, liver and stomach after acute human exposure to methyl bromide. The onset of symptoms may be delayed several hours after exposure, and recovery, when it occurs, is often prolonged

(Honma and Hasegawa, 1983; Greenburg, 1971; Torkelson et al., 1966; Longley and Simpson, 1970; Scharnweber et al., 1974; Araki et al., 1971; Ushio and Osozuka, 1977).

5.7. SUMMARY

The preliminary study of a chronic inhalation study in rats and mice is in progress (NTP, 1985). Although Danse et al. (1984) reported that 50 mg/kg/day of methyl bromide caused carcinoma of the forestomach in rats treated by gavage 5 days/week for 13 weeks, the NTP scientists that reviewed the data concluded that the rats treated with 50 mg/kg/day of methyl bromide had epithelial hyperplasia and inflammation in the forestomach, but no neoplastic lesions (U.S. EPA, 1984a, 1985). Tumors did not occur at any other dose level tested. An epidemiological study (Wong et al., 1984) suggests that occupational exposure to methyl bromide may be associated with a significantly higher incidence of testicular cancer than expected, but exposure levels were not quantified.

Methyl bromide was mutagenic to S. typhimurium strain 100, but not to strain 98, regardless of metabolic activation (Voogd et al., 1982; Moriya et al., 1983; Kramers et al., 1985; Simmon, 1978, 1981; Simmon and Tardiff, 1978; Simmon et al., 1977), to E. coli (Moriya et al., 1983; Djalali-Behzad et al., 1981) and to D. melanogaster (Voogd et al., 1982; Kramers et al., 1985; McGregor, 1981; Katz, 1985; Kramers and Bissumbhar, 1983). The only mutagenicity assay performed with mammalian cells in which methyl bromide was mutagenic is the mouse lymphoma cell assay (Voogd et al., 1982; Kramers et al., 1985). Methyl bromide did not increase unscheduled DNA synthesis (Voogd et al., 1982; Kramers et al., 1985), sperm abnormalities in mice (McGregor, 1981) or rats (McGregor, 1981) nor chromosomal abnormalities in bone marrow cells in rats (McGregor, 1981).

Methyl bromide was not teratogenic, fetotoxic or maternotoxic in rats exposed by inhalation to ≤ 70 ppm (272 mg/m³), 7 hours/day during gestation (Hardin et al., 1981; Sikov et al., 1980). In rabbits, however, methyl bromide was maternotoxic, causing a high mortality rate at an inhalation exposure concentration of 70 ppm (272 mg/m³), 7 hours/day, 5 days/week during gestation, but did not appear to be fetotoxic (Hardin et al., 1981; Sikov et al., 1980). No evidence of teratogenic effects were observed in rabbits. Pertinent data regarding other reproductive effects of methyl bromide could not be located in the available literature as cited in the Appendix.

Subchronic inhalation of methyl bromide 7.5-8 hours/day, 5 days/week resulted in convulsions, weight loss and pathological changes in the lungs of rats at 0.42 mg/l, paralysis and pulmonary disease in rabbits at ≥ 0.13 mg/l, paralysis and convulsions in monkeys at ≥ 0.25 mg/l and pulmonary lesions and death in guinea pigs at ≥ 0.42 mg/l (Irish et al., 1940). Subchronic treatment of rats by gavage 5 days/week with methyl bromide resulted in severe epithelial hyperplasia in the forestomach at a dose of 50 mg/kg/day and slight epithelial hyperplasia in the forestomach at a dose of 10 mg/kg/day (Danse et al., 1984). At 50 mg/kg/day, decreased food consumption and body weight gain, and anemia were observed in the male rats and slight pulmonary atelectasis was observed in both male and female rats (Danse et al., 1984).

6. AQUATIC TOXICITY

6.1. ACUTE

Little information is available concerning toxicity of methyl bromide to aquatic organisms. Dawson et al. (1977) reported 96-hour LC_{50} values of 11 mg/l for bluegills, Lepomis macrochirus, and 12 mg/l for tidewater silversides, Menidia beryllina. Segers et al. (1984) found that the 4-hour LC_{50} for carp, Cyprinus carpio, was 17 mg/l.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of methyl bromide to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding the effects of methyl bromide on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

Pertinent data regarding methyl bromide residues in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

Little information is available concerning effects of methyl bromide on aquatic organisms. LC_{50} values of 11, 12 and 17 mg/l have been reported for bluegills, tidewater silversides (Dawson et al., 1977) and carp, respectively (Segers et al., 1984).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

A TLV of 5 ppm (20 mg/m³), with a STEL of 15 ppm (60 mg/m³), was recommended by the ACGIH (1980) and adopted by the ACGIH (1985) to protect against the adverse neurotoxic and pulmonary effects observed after acute exposure. Methyl bromide is designated with the skin notation indicating the potential contribution of dermal absorption. The Occupational Safety and Health Administration (OSHA) standard is 20 ppm (80 mg/m³) for an 8-hour TWA exposure limit (CFR, 1985). Tolerances for methyl bromide on raw agricultural commodities range from 5 ppm on pears, apples and quinces to 300 ppm on asparagus and lettuce (U.S. EPA, 1982, 1983a,b).

An ADI of 0.021 mg/kg/day (U.S. EPA, 1985) was based on a NOAEL of 65 mg/m³ for 7.5 hours/day, 5 days/week for up to 6 months (Irish et al., 1940) and an uncertainty factor of 100. Higher doses caused adverse neurological effects (paralysis) and lung damage (U.S. EPA, 1985).

7.2. AQUATIC

Pertinent data regarding guidelines and standards for the protection of aquatic biota from the effects of methyl bromide could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Rats treated by gavage 5 days/week with 50 mg/kg/day of methyl bromide in arachis oil developed squamous cell carcinoma of the forestomach after 90 days of treatment (Danse et al., 1984). Hyperplasia (but no neoplasia) was reported at the next lower dose tested, which was 10 mg/kg/day. Reevaluation of the histopathology by NTP scientists indicated that the histological lesions reported to be squamous cell carcinoma by Danse et al. (1984) were, in fact, hyperplastic lesions (U.S. EPA, 1984a, 1985). The preliminary sub-chronic study of a chronic inhalation study in rats and mice is in progress (NTP, 1985). An epidemiology study by Wong et al. (1984) indicated that there was a significant increase in the incidence of testicular cancer among workers exposed to organic bromides, including methyl bromide. The total number of cases observed by Wong et al. (1984) was only 2, but the expected number of cases in their sample size was 0.11; the SMR was 1799 ($p < 0.05$). No exposure levels were quantitated. Methyl bromide was mutagenic in bacterial assays (Voogd et al., 1982; Moriya et al., 1983; Kramers et al., 1985; Simmon, 1978, 1981; Simmon and Tardiff, 1978; Simmon et al., 1977; Djalali-Behzad et al., 1981) and in D. melanogaster (Voogd et al., 1982; Kramers et al., 1982; McGregor, 1981; Kramers and Bissumbar, 1983). The results of mutagenicity testing in mammalian systems are inconclusive: positive results were obtained in the mouse lymphoma cell assay (Voogd et al., 1982; Kramers et al., 1982), but negative results were obtained when unscheduled DNA synthesis (Voogd et al., 1982; Kramers et al., 1982) or when sperm and chromosome abnormalities (McGregor, 1981) were measured.

Methyl bromide caused no maternal or fetal toxicity or teratogenicity in rats exposed to 20 or 70 ppm (78 or 272 mg/m³) of methyl bromide for 7

hours/day on days 1-19 of gestation and/or for 7 hours/day, 5 days/week for 3 weeks before mating (Hardin et al., 1981; Sikov, 1980). Severe maternal toxicity (96% mortality) was observed in rabbits exposed to 70 ppm (272 mg/m³) of methyl bromide, 7 hours/day on days 1-15 of gestation. No significant adverse effects were observed in rabbits exposed to 20 ppm (78 mg/m³) of methyl bromide, 7 hours/day on days 1-15 of gestation; however, the number of resorptions was slightly increased.

Groups of rats, guinea pigs, rabbits and monkeys were exposed to 0, 65, 130, 250, 420 or 850 mg/m³ of methyl bromide, 7.5 hours/day, 5 days/week for up to 6 months (Irish et al., 1940). Rats exposed to 420 mg/m³ of methyl bromide had convulsions, as did the one monkey exposed to 420 mg/m³ of methyl bromide. Although no convulsions were reported in the guinea pigs, 4/11 guinea pigs exposed to 420 mg/m³ of methyl bromide died during treatment. The exposure level of 850 mg/m³ of methyl bromide was acutely toxic to both rats and guinea pigs. The exposure level of 250 mg/m³ had no effect in rats and guinea pigs. In contrast, almost all (38/42) of the rabbits and half (3/6) the monkeys showed signs of paralysis when exposed to 250 mg/m³ of methyl bromide. Although no adverse effects were seen in monkeys exposed to 130 mg/m³, this concentration caused paralysis in all the rabbits that survived long enough for the effect to develop. Fifteen of the 58 rabbits exposed to 130 mg/m³ of methyl bromide died suddenly from a severe lung infection, probably exacerbated by methyl bromide inhalation. Adverse changes in lung histology were reported in the rabbits that were paralyzed. An exposure level of 65 mg/m³ is a NOEL for rats, guinea pigs, rabbits and monkeys and the highest NOAEL tested for rabbits. According to inhalation data, there is a steep dose-response curve and not a great difference between a NOEL and a FEL.

Two studies, one in dogs (Rosenblum et al., 1960) and another in rats (Danse et al., 1984), evaluate the oral toxicity of methyl bromide. In the Rosenberg et al. (1960) study, groups of four beagle dogs were fed methyl bromide fumigated food for 1 year so as to ingest 41.6, 89.1 or 178.2 mg/kg/day of methyl bromide, assuming all the bromide identified in the diet was present as methyl bromide. Six dogs served as controls. In this study, 41.6 and 89.1 mg/kg/day of methyl bromide had no effect. Dogs fed the high dose gained more weight and became lethargic with occasional diarrhea and excessive salivation. In the Danse et al. (1984) study, groups of 10 male and 10 female rats were treated by gavage with 0, 0.4, 2, 10 or 50 mg/kg/day of methyl bromide in arachis oil, 5 days/week for 13 weeks. No effects occurred at ≤ 2 mg/kg/day. Slight hyperplasia of the stratified squamous epithelium in the forestomach occurred in 9 females and 6 males treated with 10 mg/kg/day of methyl bromide, and severe hyperplasia of the stratified squamous epithelium in the forestomach occurred in 8 females and 10 males treated with 50 mg/kg/day methyl bromide. The other two female rats treated with 50 mg/kg/day of methyl bromide had slight epithelial hyperplasia in the forestomach. In addition, the males treated with 50 mg/kg/day of methyl bromide had anemia and significantly decreased body weights. The incidence of ateleclasis was increased in both male and female rats which, according to the investigators, may be due to methyl bromide inhaled during gavage treatment.

The subchronic oral study of Danse et al. (1984) provides the best basis for deriving an ADI for methyl bromide. The highest NOEL in the Danse et al. (1984) study is 2 mg/kg/day, 5 days/week. Higher doses cause hyperplasia in the forestomach of rats. Adverse effects were observed in dogs that ingested 178.2, but not 89.1 mg/kg/day of methyl bromide for 1 year.

Expanding the dose of 2 mg/kg/day over a 7-day week results in a dose of 1.4 mg/kg/day. An ADI of 0.0014 mg/kg/day of methyl bromide is obtained by dividing the NOEL of 1.4 mg/kg/day by an uncertainty factor of 1000 to account for interspecies extrapolation, the range of sensitivity to xenobiotics within the human population and the use of a subchronic study to derive an ADI. The ADI is equivalent to 0.098 mg/day for a 70 kg man. The ADI is provisional pending the results of the carcinogenicity study in progress (NTP, 1985).

The previously determined ADI of 0.021 mg/kg/day (U.S. EPA, 1982, 1985) was based on the inhalation study in rats, guinea pigs, rabbits and monkeys (Irish et al., 1940) in which no adverse effects were observed in rabbits exposed to 65 mg/m³ of methyl bromide for 7.5 hours/day, 5 days/week for 6 months. The next higher dose level, 250 mg/m³, resulted in paralysis and pulmonary damage in rabbits. The values for human daily breathing volume (20 m³/day); the human body weight (70 kg), and an uncertainty factor of 100 to account for interspecies extrapolation and the range of sensitivity to xenobiotics within the human population, were used to obtain an ADI of 0.021 mg/kg/day. The pharmacokinetic data of Medinsky et al. (1984) indicate that enterohepatic recirculation plays a major role in the fate of methyl bromide after oral administration. Furthermore, the neurological effects (convulsions in rats and monkeys, paralysis in rabbits and monkeys ataxia and headache in humans) reported after inhalation exposure did not occur in the rats and dogs treated orally. On a mg/kg/day basis, assuming an absorption rate of 50%, which is experimentally supported by the data of Medinsky et al. (1985), the oral dose was larger than the inhalation dose. Therefore, based on the pharmacokinetic data and the adverse effects produced, it is not advisable to derive an oral ADI for methyl bromide based on inhalation studies.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

As summarized in Table 9-1, three studies are used in the derivation of the RQ. Groups of 10 male and 10 female rats were treated by gavage with 0, 0.4, 2, 10 or 50 mg/kg/day of methyl bromide in arachis oil, 5 days/week for 13 weeks (Danse et al., 1984). Hyperplasia of the forestomach occurred in the rats treated with 10 and 50 mg/kg/day. Male rats treated with 50 mg/kg/day had significantly decreased body weight and anemia. Both males and females treated with 50 mg/kg/day had adverse changes in lung histology including alveolar necrosis.

Groups of four beagle dogs were fed methyl bromide fumigated food for 1 year so as to ingest 41.6, 89.1 or 178.2 mg/kg/day methyl bromide, assuming all the bromide identified in the diet was present as methyl bromide (Rosenblum et al., 1960). Six dogs served as controls. At the highest dose, the dogs became lethargic, occasionally had diarrhea and excessive salivation, and had significantly increased body weights. No other adverse effects were reported.

Groups of rats, guinea pigs, rabbits and monkeys were exposed to 0, 65, 130, 250 420 or 850 mg/m³ of methyl bromide, 7.5 hours/day, 5 days/week for up to 6 months (Irish et al., 1940). An exposure level of 850 mg/m³ was acutely toxic to rats and guinea pigs. An exposure level of 420 mg/m³ was acutely toxic to some rats, caused convulsions in subchronically exposed rats, and adverse changes in lung histology. Exposure levels of 250 and 130 mg/m³ resulted in paralysis and adverse changes in lung histology, including alveolar necrosis, in rabbits. Paralysis occurred in monkeys, after 25-45 exposures at the 250 mg/m³ level.

TABLE 9-1
Toxicity Summary for Methyl Bromide

Route	Species/ Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Gavage	rat/Wistar	M/F	10/10	0.35 ^a	arachnis oil	>98%	10 mg/kg/day 5 days/week for 13 weeks	7 ^b	Epithelial hyperplasia in the forestomach	Danse et al., 1984
Gavage	rat/Wistar	M	10	0.35 ^a	arachnis oil	>98%	50 mg/kg/day 5 days/week for 13 weeks	3 ^b	Decreased body weight and anemia in the males; atelec- tasis in both males and females; epithelial hyper- plasia in the forestomach of male and female rats.	Danse et al., 1984
Diet	dog/Beagle	M/F	4	12.1 ^c	In food	NR	178.2 mg/kg/day for 1 year	178.2	Lethargy	Rosenblum et al., 1960
Inhalation	rabbit	M/F	50	3.8 ^d	NR		130 mg/m ³ 7.5 hours/day, 5 days/week for 6 months	15.3 ^e	Paralysis in 34; 15 died or were killed when moribund from a lung infection; 1 died in pregnancy; 8 were sacrificed "before they showed any reaction;" adverse changes in lung histology in rabbits with paralysis	Irish et al., 1940
Inhalation	rat	M/F	30	0.35 ^a	NR		420 mg/m ³ 7.5 hours/day, 5 days/week for 6 months	59.7 ^e	Convulsions; adverse changes in lung histology	Irish et al., 1940

^aReference rat body weight from U.S. EPA, 1980

^bDose calculated by expanding the experimental dose over a 7-day week.

^cAverage weight determined from data provided by investigator

^dReference rabbit body from Durkin, 1985

^eDose calculated by expanding exposure over a 24-hour day and a 7-day week by multiplying by the rabbit (Durkin, 1985) or the rat (U.S. EPA, 1980) inhala-
tion rates and dividing by the animal body weight.

NR = Not reported

Data used to calculate the CSs are presented in Table 9-2. The MEDs were obtained by dividing the animal doses by an uncertainty factor of 10 to account for the use of subchronic studies to derive a chronic RQ, and by multiplying the cube root of the ratio of the animal body weight (see Table 9-1) to the reference man body weight of 70 kg (U.S. EPA, 1980) by 70 kg. The RV_e of 4 is appropriate for the hyperplasia observed in the forestomach of the rats treated with 10 mg/kg/day of methyl bromide. Of the effects observed in rats treated orally with 50 mg/kg/day of methyl bromide, including decreased body weight, forestomach hyperplasia, anemia and atelectasis, atelectasis was used to derive the RQ because it is the most severe effect and is associated with an RV_e of 7. Of the effects observed in dogs treated orally with 178.2 mg/kg/day of methyl bromide, lethargy was the most severe and is associated with an RV_e of 6. Similarly, of the effects observed in rabbits after inhalation of 130 mg/m³ of methyl bromide, including paralysis and adverse histological changes in the lungs, paralysis is the more severe and is associated with an RV_e of 9. Finally, the RV_e of 9 associated with convulsions is higher than the RV_e associated with adverse changes in lung histology and, therefore, was used in rating the effects observed in rats exposed to 420 mg/m³ of methyl bromide. The CS, in each case, is derived by multiplying the RV_d by the RV_e . The highest CS (27.9) which corresponds to an RQ of 100 is obtained from the inhalation exposure of rabbits to 130 mg/m³ of methyl bromide (Irish et al., 1940) (see Table 9-2). Therefore, the data for paralysis in rabbits exposed by inhalation in the Irish et al. (1940) study is recommended as the basis for the RQ for methyl bromide (Table 9-3).

TABLE 9-2
Composite Scores for Methyl Bromide

Route	Species	Transformed Animal Dose (mg/kg/day)	Human MCD (mg/day)*	RV _d	Effect	RV _e	CS	RQ	Reference
Gavage	rat	7.1	8.5	4.1	epithelial hyperplasia in the forestomach	4	16.4	1000	Danse et al., 1984
Gavage	rat	36.0	43.1	3.0	atelectasis	7	21	100	Danse et al., 1984
Diet	dog	178.2	695	1.2	lethargy	6	7.2	1000	Rosenblum et al., 1960
Inhalation	rabbit	15.3	40.1	3.1	paralysis	9	27.9	100	Irish et al., 1940
Inhalation	rat	59.7	71.5	2.7	convulsions	9	24.3	100	Irish et al., 1940

*The doses were divided by an uncertainty factor of 10 to approximate chronic exposure.

TABLE 9-3

Methyl Bromide

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose:	40.1
Effect:	paralysis
Reference:	Irish et al., 1940
RV _d :	3.1
RV _e :	9
Composite Score:	27.9
RQ:	100

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The carcinogenicity of inhalation exposure to methyl bromide is being tested in rats and mice by the National Toxicology Program, and the preliminary subchronic studies are in progress (NTP, 1985).

In a preliminary assessment of methyl bromide carcinogenicity (Holder, 1984), it was noted that methyl bromide is similar chemically in structure and in methylating ability to methyl chloride and methyl iodide both of which are suspected carcinogenic compounds. It was recommended, however, that classification of methyl bromide await the results of further studies.

Although Danse et al. (1984) reported that there was a significant increase in the incidence of squamous cell carcinoma in the forestomach of rats treated by gavage with 50 mg/kg/day of methyl bromide, 5 days/week for 90 days, the NTP scientists who reevaluated the histological slides concluded that the lesions reported in the rats treated with 50 mg/kg/day of methyl bromide by Danse et al. (1984) were, in fact, hyperplastic lesions and not neoplastic lesions (U.S. EPA, 1984a, 1985). Therefore, the evidence from animal studies is inadequate. An epidemiological study by Wong et al. (1984) indicated that there was a higher mortality rate from testicular cancer among workers potentially exposed to methyl bromide than expected (see Table 5-1). Although the human data are suggestive of a carcinogenic effect. The data are inadequate because of confounding exposure to other organic bromides, some of which are suspected carcinogens, and since no exposure levels were quantified. Therefore, an F-factor could not be calculated. Because of this limited evidence in humans and animals, methyl bromide should be placed in EPA Group D for carcinogenicity (U.S. EPA, 1984b), which indicates the data for methyl bromide are inadequate to

determine its carcinogenicity. This indicates that methyl bromide has a low hazard ranking under CERCLA. This classification of carcinogenicity may change pending the results of the chronic inhalation bioassay in rats and mice (NTP, 1985).

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CAS online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

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